

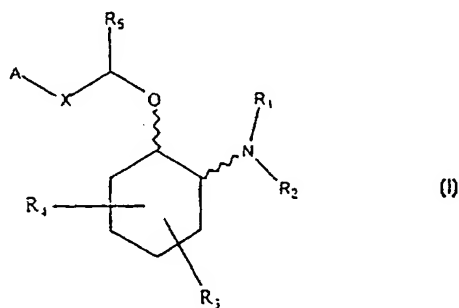
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(54) Title: AMINOCYCLOHEXYL ETHER COMPOUNDS AND USES THEREOF



(57) Abstract

Aminocyclohexyl ether compounds of formula (I), or a solvate or pharmaceutically acceptable salt thereof are disclosed. In said formula, A, X and R, -R₅ have the meanings given in the description. The compounds of the present invention may be incorporated in compositions and kits. The present invention also discloses a variety of *in vitro* and *in vivo* uses for the compounds and compositions, including the treatment of arrhythmia and the production of analgesia and local anesthesia.

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AMINOCYCLOHEXYL ETHER COMPOUNDS AND USES THEREOF

TECHNICAL FIELD

The present invention is generally directed toward aminocyclohexyl ether compounds, pharmaceutical compositions and kits containing the
5 aminocyclohexyl ether compounds, and therapeutic uses thereof.

BACKGROUND OF THE INVENTION

Arrhythmia is a variation from the normal rhythm of the heart beat and generally represents the end product of abnormal ion-channel structure, number or function. Both atrial arrhythmias and ventricular arrhythmias are known. The major
10 cause of fatalities due to cardiac arrhythmias is the subtype of ventricular arrhythmias known as ventricular fibrillation (VF). Conservative estimates indicate that, in the U.S. alone, each year over one million Americans will have a new or recurrent coronary attack (defined as myocardial infarction or fatal coronary heart disease). About 650,000 of these will be first heart attacks and 450,000 will be recurrent attacks. About one-
15 third of the people experiencing these attacks will die of them. At least 250,000 people a year die of coronary heart disease with 1 hour of the onset of symptoms and before they reach a hospital. These are sudden deaths caused by cardiac arrest, usually resulting from ventricular fibrillation.

Atrial fibrillation (AF) is the most common arrhythmia seen in clinical
20 practice and is a cause of morbidity in many individuals (Pritchett E.L., *N. Engl. J. Med.* 327(14):1031 Oct. 1, 1992, discussion 1031-2; Kannel and Wolf, *Am. Heart J.* 123(1):264-7 Jan. 1992). Its prevalence is likely to increase as the population ages and it is estimated that 3-5% of patients over the age of 60 years have AF (Kannel W.B., Abbot R.D., Savage D.D., McNamara P.M., *N. Engl. J. Med.* 306(17):1018-22, 1982;
25 Wolf P.A., Abbot R.D., Kannel W.B. *Stroke*. 22(8):983-8, 1991). While AF is rarely fatal, it can impair cardiac function and is a major cause of stroke (Hinton R.C., Kistler J.P., Fallon J.T., Friedlich A.L., Fisher C.M., *American Journal of Cardiology* 40(4):509-13, 1977; Wolf P.A., Abbot R.D., Kannel W.B., *Archives of Internal*

Medicine 147(9):1561-4, 1987; Wolf P.A., Abbot R.D., Kannel W.B. *Stroke*. 22(8):983-8, 1991; Cabin H.S., Clubb K.S., Hall C., Perlmutter R.A., Feinstein A.R., *American Journal of Cardiology* 65(16):1112-6, 1990).

Antiarrhythmic agents have been developed to prevent or alleviate cardiac arrhythmia. For example, Class I antiarrhythmic compounds have been used to treat supraventricular arrhythmias and ventricular arrhythmias. Treatment of ventricular arrhythmia is very important since such an arrhythmia can be fatal. Serious ventricular arrhythmias (ventricular tachycardia and ventricular fibrillation) occur most often in the presence of myocardial ischemia and/or infarction. Ventricular fibrillation often occurs in the setting of acute myocardial ischemia, before infarction fully develops. At present, there is no satisfactory pharmacotherapy for the treatment and/or prevention of ventricular fibrillation during acute ischemia. In fact, many Class I antiarrhythmic compounds may actually increase mortality in patients who have had a myocardial infarction.

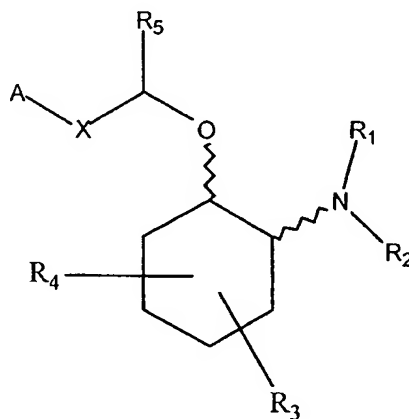
Class Ia, Ic and III antiarrhythmic drugs have been used to convert recent onset AF to sinus rhythm and prevent recurrence of the arrhythmia (Fuch and Podrid, 1992; Nattel S., Hadjis T., Talajic M., *Drugs* 48(3):345-71, 1994). However, drug therapy is often limited by adverse effects, including the possibility of increased mortality, and inadequate efficacy (Feld G.K., *Circulation*. 83(6):2248-50, 1990; Coplen S.E., Antman E.M., Berlin J.A., Hewitt P., Chalmers T.C., *Circulation* 1991; 83(2):714 and *Circulation* 82(4):1106-16, 1990; Flaker G.C., Blackshear J.L., McBride R., Kronmal R.A., Halperin J.L., Hart R.G., *Journal of the American College of Cardiology* 20(3):527-32, 1992; CAST, *N. Engl. J. Med.* 321:406, 1989; Nattel S., *Cardiovascular Research*. 37(3):567-77, 1998). Conversion rates for Class I antiarrhythmics range between 50-90% (Nattel S., Hadjis T., Talajic M., *Drugs* 48(3):345-71, 1994; Steinbeck G., Remp T., Hoffmann E., *Journal of Cardiovascular Electrophysiology*. 9(8 Suppl):S104-8, 1998). Class III antiarrhythmics appear to be more effective for terminating atrial flutter than for AF and are generally regarded as less effective than Class I drugs for terminating of AF (Nattel S., Hadjis T., Talajic M., *Drugs*. 48(3):345-71, 1994; Capucci A., Aschieri D., Villani G.Q., *Drugs & Aging*

13(1):51-70, 1998). Examples of such drugs include ibutilide, dofetilide and sotalol. Conversion rates for these drugs range between 30-50% for recent onset AF (Capucci A., Aschieri D., Villani G.Q., *Drugs & Aging* 13(1):51-70, 1998), and they are also associated with a risk of the induction of Torsades de Pointes ventricular
 5 tachyarrhythmias. For ibutilide, the risk of ventricular proarrhythmia is estimated at ~4.4%, with ~1.7% of patients requiring cardioversion for refractory ventricular arrhythmias (Kowey P.R., VanderLugt J.T., Luderer J.R., *American Journal of Cardiology* 78(8A):46-52, 1996). Such events are particularly tragic in the case of AF as this arrhythmia is rarely a fatal in and of itself.

10 Therefore, there is a need in the art to identify new antiarrhythmic treatments, for both ventricular arrhythmias as well as for atrial arrhythmias. The present invention fulfills this need, and further provides other related advantages.

SUMMARY OF THE INVENTION

In one embodiment, the present invention provides aminocyclohexyl
 15 ether compounds of formula (I), or a solvate or pharmaceutically acceptable salt thereof:



(I)

wherein, independently at each occurrence,

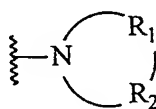
20 X is selected from a direct bond, -C(R₆,R₁₄)-Y- and -C(R₁₃)=CH-;

Y is selected from a direct bond, O, S and C₁-C₄alkylene;

R_{13} is selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl and benzyl;

R_1 and R_2 are independently selected from hydrogen, C_1 - C_8 alkyl, C_3 - C_8 alkoxyalkyl, C_1 - C_8 hydroxyalkyl, and C_7 - C_{12} aralkyl; or

- 5 R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (I), form a ring denoted by formula (II):



(II)

- 10 wherein the ring of formula (II) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy,
- 15 C_1 - C_3 hydroxyalkyl, oxo, C_2 - C_4 acyl, C_1 - C_3 alkyl, C_2 - C_4 alkylcarboxy, C_1 - C_3 alkoxy, C_1 - C_{20} alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C_3 - C_8 carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with
- 20 substituents selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_4 acyl, C_2 - C_4 hydroxyalkyl and C_3 - C_8 alkoxyalkyl; or

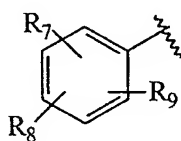
- R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]-
- 25 hexan-3-yl and 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring shown in formula (I) at the 3-, 4-, 5- or 6- positions and are independently selected from hydrogen, hydroxy, C_1 - C_6 alkyl and C_1 - C_6 alkoxy, and, when both R_3 and R_4 are attached

to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur;

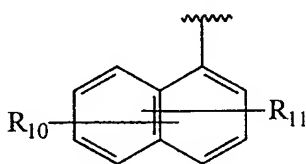
R_5 , R_6 and R_{14} are independently selected from hydrogen, C_1 - C_6 alkyl, aryl and benzyl, or R_6 and R_{14} , when taken together with the carbon to which they are
5 attached, may form a spiro C_3 - C_5 cycloalkyl;

A is selected from C_5 - C_{12} alkyl, a C_3 - C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII) and (VIII):



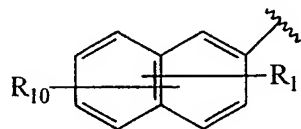
(III)

where R_7 , R_8 and R_9 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, aryl and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are
15 independently selected from hydrogen, acetyl, methanesulfonyl and C_1 - C_6 alkyl;



(IV)

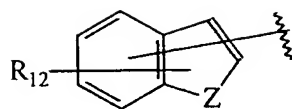
and



(V)

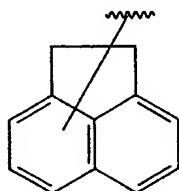
where R_{10} and R_{11} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are
20 independently selected from hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl;

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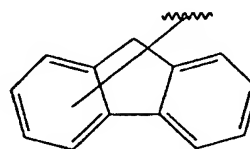


(VI)

where R₁₂ is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C₂-C₇alkanoyloxy, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₇alkoxycarbonyl, C₁-C₆thioalkyl, and N(R₁₅,R₁₆) where R₁₅ and R₁₆ are independently selected from hydrogen, acetyl, methanesulfonyl, and C₁-C₆alkyl; and Z is selected from CH, CH₂, O, N and S, where Z may be directly bonded to "X" as shown in formula (I) when Z is CH or N, or Z may be directly bonded to R₁₇ when Z is N, and R₁₇ is selected from hydrogen, C₁-C₆alkyl, C₃-C₈cycloalkyl, aryl and benzyl;



(VII)



(VIII)

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

In other embodiments, the present invention provides a composition or medicament that includes a compound according to formula (I) in combination with a pharmaceutically acceptable carrier, diluent or excipient, and further provides a method for the manufacture of a composition or medicament that contains a compound according to formula (I).

In other embodiments, the present invention provides pharmaceutical compositions that contain at least one compound of formula (I) in an amount effective to treat a disease or condition in a warm-blooded animal suffering from or having the disease or condition, and/or prevent a disease or condition in a warm-blooded animal that would otherwise occur, and further contains at least one pharmaceutically acceptable carrier, diluent or excipient. The invention further provides for methods of treating a disease or condition in a warm-blooded animal suffering from or having the

disease or condition, and/or preventing a disease or condition from arising in a warm-blooded animal, wherein a therapeutically effective amount of a compound of formula (I), or a composition containing a compound of formula (I) is administered to a warm-blooded animal in need thereof. The diseases and conditions to which the compounds, compositions and methods of the present invention have applicability are as follows: arrhythmia, diseases of the central nervous system, convulsion, epileptic spasms, depression, anxiety, schizophrenia, Parkinson's disease, respiratory disorders, cystic fibrosis, asthma, cough, inflammation, arthritis, allergies, gastrointestinal disorders, urinary incontinence, irritable bowel syndrome, cardiovascular diseases, cerebral or myocardial ischemias, hypertension, long-QT syndrome, stroke, migraine, ophthalmic diseases, diabetes mellitus, myopathies, Becker's myotonia, myasthenia gravis, paramyotonia congenita, malignant hyperthermia, hyperkalemic periodic paralysis, Thomsen's myotonia, autoimmune disorders, graft rejection in organ transplantation or bone marrow transplantation, heart failure, hypotension, Alzheimer's disease or other metal disorder, and alopecia.

In another embodiment, the present invention provides a pharmaceutical composition containing an amount of a compound of formula (I) effective to produce local analgesia or anesthesia in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The invention further provides a method for producing, local analgesia or anesthesia in a warm-blooded animal which includes administering to a warm-blooded animal in need thereof an effective amount of a compound of formula (I) or a pharmaceutical composition containing a compound of formula (I). These compositions and methods may be used to relieve or forestall the sensation of pain in a warm-blooded animal.

In another embodiment, the present invention provides a pharmaceutical composition containing an amount of a compound of formula (I) effective to enhance the libido in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient. The invention further provides a method for enhancing libido in a warm-blooded animal which includes administering to a warm-blooded animal in need thereof an effective amount of a compound of formula (I) or a

pharmaceutical composition containing a compound of formula (I). These compositions and methods may be used, for example, to treat a sexual dysfunction, *e.g.*, impotence in males, and/or to enhance the sexual desire of a patient without a sexual dysfunction. As another example, the therapeutically effective amount may be administered to a bull (or other breeding stock), to promote increased semen ejaculation, where the ejaculated semen is collected and stored for use as it is needed to impregnate female cows in promotion of a breeding program.

In another embodiment, the present invention provides a compound of formula (I) or composition containing a compound of formula (I), for use in methods for either modulating ion channel activity in a warm-blooded animal or for modulating ion channel activity *in vitro*.

These and other embodiments of the present invention will become evident upon reference to the following drawings and detailed description.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 illustrates the reaction sequence further described in Example 1, for preparing an aminocyclohexyl ether compound of the present invention.

Figure 2 illustrates a procedure whereby either *cis*- or *trans*-aminocyclohexyl ether compounds of the present invention may be prepared.

Figure 3 illustrates synthetic methodology that may be employed to prepare either *cis* or *trans* stereoisomers of the compounds of the present invention.

Figures 4A and 4B illustrate the synthetic methodology described in Example 15.

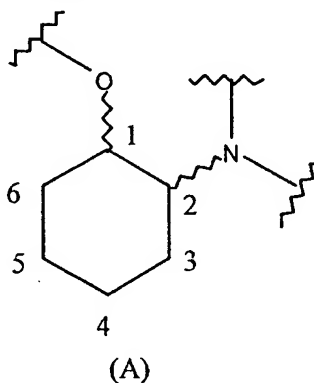
DETAILED DESCRIPTION OF THE INVENTION

As noted above, the present invention is directed to aminocyclohexyl ether compounds, pharmaceutical compositions containing the aminocyclohexyl ether compounds, and various uses for the compound and compositions. Such uses include blockage of ion channels *in vitro* or *in vivo*, the treatment of arrhythmias, the production of anesthesia, and other uses as described herein. An understanding of the present

invention may be aided by reference to the following definitions and explanation of conventions used herein.

Definitions and Conventions

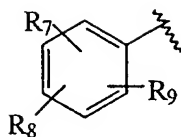
The aminocyclohexyl ether compounds of the invention have an ether oxygen atom at position 1 of a cyclohexane ring, and an amine nitrogen atom at position 2 of the cyclohexane ring, with other positions numbered in corresponding order as shown below in structure (A):



The bonds from the cyclohexane ring to the 1-oxygen and 2-nitrogen atoms in the above formula may be relatively disposed in either a *cis* or *trans* relationship. In a preferred embodiment of the present invention, the stereochemistry of the amine and ether substituents of the cyclohexane ring is either (R,R)-*trans* or (S,S)-*trans*. In another preferred embodiment the stereochemistry is either (R,S)-*cis* or (S,R)-*cis*.

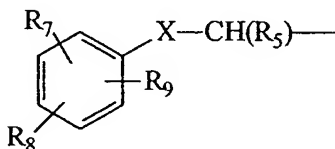
In the formulae depicted herein, a bond to a substituent and/or a bond that links a molecular fragment to the remainder of a compound may be shown as intersecting one or more bonds in a ring structure. This indicates that the bond may be attached to any one of the atoms that constitutes the ring structure, so long as a hydrogen atom could otherwise be present at that atom. Where no particular substituent(s) is identified for a particular position in a structure, then hydrogen(s) is present at that position. For example, compounds of the invention containing the A-X-CH(R₃)- group where A equals formula (III)

10



(III)

are intended to encompass compounds having the group (B):

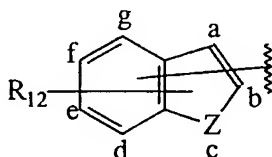


(B)

where the group (B) is intended to encompass groups wherein any ring atom that could otherwise be substituted with hydrogen, may instead be substituted with either R_7 , R_8 or R_9 , with the proviso that each of R_7 , R_8 and R_9 appears once and only once on the ring.

- 10 Ring atoms that are not substituted with any of R_7 , R_8 or R_9 are substituted with hydrogen. In those instances where the invention specifies that a non-aromatic ring is substituted with more than one R group, and those R groups are shown connected to the non-aromatic ring with bonds that bisect ring bonds, then the R groups may be present at different atoms of the ring, or on the same atom of the ring, so long as that atom
- 15 could otherwise be substituted with a hydrogen atom.

Likewise, where the invention specifies compounds containing the A-X-CH(R_5)- group where A equals the aryl group (VI)



(VI)

the invention is intended to encompass compounds wherein -X-CH(R_5)- is joined through X to the aryl group (VI) at any atom which forms the aryl group (VI) so long as that atom of group (VI) could otherwise be substituted with a hydrogen atom. Thus, there are seven positions (identified with the letters "a" through "g") in structure (VI)

- 25 where the -X-CH(R_5)- group could be attached, and it is attached at one of those seven

positions. The R_{12} group would occupy one and only one of the remaining six positions, and hydrogen atoms would be present in each of the five remaining positions. It is to be understood that when Z represents a divalent atom, *e.g.*, oxygen or sulfur, then Z cannot be directly bonded to $-X-CH(R_5)-$.

5 When the invention specifies the location of an asymmetric divalent radical, then that divalent radical may be positioned in any possible manner that provides a stable chemical structure. For example, for compounds containing the $A-X-CH(R_5)-$ group where X is $C(R_{14}, R_6)-Y-$, the invention provides compounds having both the $A-C(R_{14}, R_6)-Y-CH(R_5)-$ and $A-Y-C(R_{14}, R_6)-CH(R_5)-$ groups.

10 A wavy bond from a substituent to the central cyclohexane ring indicates that that group may be located on either side of the plane of the central ring.

 The compounds of the present invention contain at least two asymmetric carbon atoms and thus exist as enantiomers and diastereomers. Unless otherwise noted, the present invention includes all enantiomeric and diastereomeric forms of the
15 aminocyclohexyl ether compounds of the invention. Pure stereoisomers, mixtures of enantiomers and/or diastereomers, and mixtures of different compounds of the invention are included within the present invention. Thus, compounds of the present invention may occur as racemates, racemic mixtures and as individual diastereomers, or enantiomers with all isomeric forms being included in the present invention. A
20 racemate or racemic mixture does not imply a 50:50 mixture of stereoisomers.

 The phrase "independently at each occurrence" is intended to mean (i) when any variable occurs more than one time in a compound of the invention, the definition of that variable at each occurrence is independent of its definition at every other occurrence; and (ii) the identity of any one of two different variables (*e.g.*, R_1
25 within the set R_1 and R_2) is selected without regard the identity of the other member of the set. However, combinations of substituents and/or variables are permissible only if such combinations result in stable compounds.

 In accordance with the present invention and as used herein, the following terms are defined to have following meanings, unless explicitly stated
30 otherwise:

“Acid addition salts” refers to those salts which retain the biological effectiveness and properties of the free bases and which are not biologically or otherwise undesirable, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid and the like, or organic acids such as acetic acid, propionic acid, glycolic acid, pyruvic acid, oxalic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, *p*-toluenesulfonic acid, salicylic acid and the like.

“Acyl” refers to branched or unbranched hydrocarbon fragments terminated by a carbonyl $-(C=O)-$ group containing the specified number of carbon atoms. Examples include acetyl $[CH_3C=O-]$, a C_2 acyl and propionyl $[CH_3CH_2C=O-]$, a C_3 acyl.

“Alkanoyloxy” refers to an ester substituent wherein the ether oxygen is the point of attachment to the molecule. Examples include propanoyloxy $[(CH_3CH_2C=O-O-)]$, a C_3 alkanoyloxy and ethanoyloxy $[CH_3C=O-O-]$, a C_2 alkanoyloxy.

“Alkoxy” refers to an O-atom substituted by an alkyl group, for example, methoxy $[-OCH_3]$, a C_1 alkoxy.

“Alkoxyalkyl” refers to a alkylene group substituted with an alkoxy group. For example, methoxyethyl $[CH_3OCH_2CH_2-]$ and ethoxymethyl $[CH_3CH_2OCH_2-]$ are both C_3 alkoxyalkyl groups.

“Alkoxycarbonyl” refers to an ester substituent wherein the carbonyl carbon is the point of attachment to the molecule. Examples include ethoxycarbonyl $[CH_3CH_2OC=O-]$, a C_3 alkoxycarbonyl and methoxycarbonyl $[CH_3OC=O-]$, a C_2 alkoxycarbonyl.

“Alkyl” refers to a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms and having one point of attachment. Examples include *n*-propyl (a C_3 alkyl), *iso*-propyl (also a C_3 alkyl), and *t*-butyl (a C_4 alkyl).

"Alkylene" refers to a divalent radical which is a branched or unbranched hydrocarbon fragment containing the specified number of carbon atoms, and having two points of attachment. An example is propylene [-CH₂CH₂CH₂-, a C₃alkylene].

"Alkylcarboxy" refers to a branched or unbranched hydrocarbon
5 fragment terminated by a carboxylic acid group [-COOH]. Examples include carboxymethyl [HOOC-CH₂-, a C₂alkylcarboxy] and carboxyethyl [HOOC-CH₂CH₂-, a C₃alkylcarboxy].

"Aryl" refers to aromatic groups which have at least one ring having a conjugated pi electron system and includes carbocyclic aryl, heterocyclic aryl (also
10 known as heteroaryl groups) and biaryl groups, all of which may be optionally substituted. Carbocyclic aryl groups are generally preferred in the compounds of the present invention, where phenyl and naphthyl groups are preferred carbocyclic aryl groups.

"Aralkyl" refers to an alkylene group wherein one of the points of
15 attachment is to an aryl group. An example of an aralkyl group is the benzyl group [C₆H₅CH₂-, a C₇aralkyl group].

"Cycloalkyl" refers to a ring, which may be saturated or unsaturated and monocyclic, bicyclic, or tricyclic formed entirely from carbon atoms. An example of a cycloalkyl group is the cyclopentenyl group (C₅H₇-), which is a five carbon (C₅)
20 unsaturated cycloalkyl group.

"Carbocyclic" refers to a ring which may be either an aryl ring or a cycloalkyl ring, both as defined above.

"Carbocyclic aryl" refers to aromatic groups wherein the atoms which form the aromatic ring are carbon atoms. Carbocyclic aryl groups include monocyclic
25 carbocyclic aryl groups such as phenyl, and bicyclic carbocyclic aryl groups such as naphthyl, all of which may be optionally substituted.

"Heteroatom" refers to a non-carbon atom, where boron, nitrogen, oxygen, sulfur and phosphorus are preferred heteroatoms, with nitrogen, oxygen and sulfur being particularly preferred heteroatoms in the compounds of the present
30 invention.

"Heteroaryl" refers to aryl groups having from 1 to 9 carbon atoms and the remainder of the atoms are heteroatoms, and includes those heterocyclic systems described in "Handbook of Chemistry and Physics," 49th edition, 1968, R.C. Weast, editor; The Chemical Rubber Co., Cleveland, OH. See particularly Section C, Rules for
5 Naming Organic Compounds, B. Fundamental Heterocyclic Systems. Suitable heteroaryls include furanyl, thienyl, pyridyl, pyrrolyl, pyrimidyl, pyrazinyl, imidazolyl, and the like.

"Hydroxyalkyl" refers to a branched or unbranched hydrocarbon fragment bearing an hydroxy (-OH) group. Examples include hydroxymethyl
10 (-CH₂OH, a C₁hydroxyalkyl) and 1-hydroxyethyl (-CHOHCH₃, a C₂hydroxyalkyl).

"Thioalkyl" refers to a sulfur atom substituted by an alkyl group, for example thiomethyl (CH₃S-, a C₁thioalkyl).

"Modulating" in connection with the activity of an ion channel means that the activity of the ion channel may be either increased or decreased in response to
15 administration of a compound or composition or method of the present invention. Thus, the ion channel may be activated, so as to transport more ions, or may be blocked, so that fewer or no ions are transported by the channel.

"Pharmaceutically acceptable carriers" for therapeutic use are well known in the pharmaceutical art, and are described, for example, in Remingtons
20 Pharmaceutical Sciences, Mack Publishing Co. (A.R. Gennaro edit. 1985). For example, sterile saline and phosphate-buffered saline at physiological pH may be used. Preservatives, stabilizers, dyes and even flavoring agents may be provided in the pharmaceutical composition. For example, sodium benzoate, sorbic acid and esters of *p*-hydroxybenzoic acid may be added as preservatives. Id. at 1449. In addition,
25 antioxidants and suspending agents may be used. Id.

"Pharmaceutically acceptable salt" refers to salts of the compounds of the present invention derived from the combination of such compounds and an organic or inorganic acid (acid addition salts) or an organic or inorganic base (base addition salts). The compounds of the present invention may be used in either the free base or

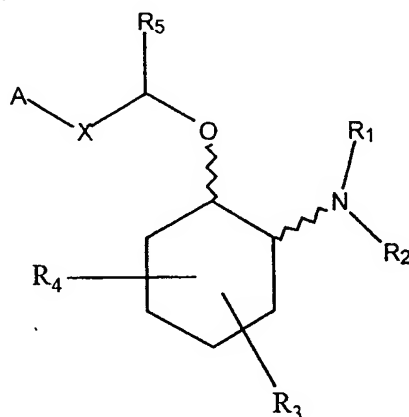
salt forms, with both forms being considered as being within the scope of the present invention.

The "therapeutically effective amount" of a compound of the present invention will depend on the route of administration, the type of warm-blooded animal being treated, and the physical characteristics of the specific warm-blooded animal under consideration. These factors and their relationship to determining this amount are well known to skilled practitioners in the medical arts. This amount and the method of administration can be tailored to achieve optimal efficacy but will depend on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

Compositions described herein as "containing a compound of formula (I)" encompass compositions that contain more than one compound of formula (I).

Compounds of the Present Invention

The compounds of the present invention are amines which may be represented by formula (I):



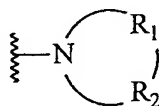
(I)

Compounds of formula (I) are aminocyclohexyl ethers. More specifically, these aminocyclohexyl ethers are substituted at position 2 of the cyclohexyl ring with an amine group -NR₁R₂. The cyclohexyl ring may also be substituted with additional

substituents (designated as R_3 and R_4) as described in more detail below. Examples of specific embodiments of compounds represented by formula (I) are described below

Depending upon the selection of substituents R_1 and R_2 , the compounds of formula (I) may be primary, secondary, or tertiary amines (*i.e.*, both R_1 and R_2 are hydrogen, only one of R_1 and R_2 is hydrogen, or neither of R_1 and R_2 are hydrogen, respectively). Where the amine is tertiary, it may be a cyclic amine. Amine substituents R_1 and R_2 may be independently selected from substituents which include hydrogen, alkyl groups containing from one to eight carbon atoms (*i.e.*, C_1 - C_8 alkyl), alkoxyalkyl groups containing from three to eight carbon atoms (*i.e.*, C_3 - C_8 alkoxyalkyl), alkyl groups containing from one to eight carbon atoms where one of the carbon atoms is substituted with a hydroxyl group (*i.e.*, C_1 - C_8 hydroxyalkyl), and aralkyl groups containing from seven to twelve carbon atoms (*i.e.*, C_7 - C_{12} aralkyl).

Alternatively, R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a ring denoted by formula (II):



(II)

wherein the ring of formula (II) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C_1 - C_3 hydroxyalkyl, oxo, C_2 - C_4 acyl, C_1 - C_3 alkyl, C_2 - C_4 alkylcarboxy, C_1 - C_3 alkoxy, C_1 - C_{20} alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur (*e.g.*, an acetal, thioacetal, ketal, or thioketal group); and any two adjacent additional carbon ring atoms may be fused to a C_3 - C_8 carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_4 acyl, C_2 - C_4 hydroxyalkyl and C_3 - C_8 alkoxyalkyl. Examples

of substituents containing a fused ring system include the perhydroindolyl and 1,2,3,4-tetrahydroisoquinoliny groups.

In connection with the ring of formula (II), any two adjacent ring atoms may be joined together by single or double bonds. Thus, the ring of formula (II) may be
5 saturated or unsaturated, and an unsaturated ring may contain one, or more than one, sites of unsaturation. In other words, the ring of formula (II) may contain one or more double bonds, it being understood, however, that the unsaturated ring of formula (II) is chemically stable.

Alternatively, R_1 and R_2 , when taken together with the 2-amino nitrogen
10 of formula (I), may complete a bicyclic ring. Bicyclic rings include, for example, 3-azabicyclo[3.2.2]nonane, 2-azabicyclo[2.2.2]octane, 3-azabicyclo[3.1.0]hexane, and 3-azabicyclo[3.2.0]heptane. For these derivatives, the 2-substituents of the cyclohexyl ethers of formula (I) are the following groups: 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]-
15 heptan-3-yl.

Preferably, R_1 and R_2 , when taken together, contain only a single heteroatom. Preferred heteroatoms include nitrogen, oxygen and sulfur. An example of a ring in which R_1 and R_2 together include an oxygen heteroatom is the morpholinyl group. An example of a ring where R_1 and R_2 together include a second nitrogen
20 heteroatom is the piperazinyl group.

Cyclohexane substituents R_3 and R_4 may be independently attached to ring positions 3, 4, 5 or 6 (*i.e.*, both R_3 and R_4 may be attached to the same ring position or each attached to different ring positions). R_3 and R_4 are independently selected from hydrogen, hydroxy, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy, and, when both R_3 and R_4 are attached
25 to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur. Preferred heterocyclic substituents contain either a single oxygen or a single sulfur ring atom.

Depending upon the identity of X, the ether side chain, $-CH(R_5)-X-A$, in
30 formula (I) may take several forms. For example, a compound of formula (I) may have

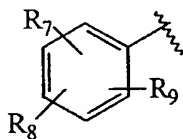
X as a $-C(R_6, R_{14})-Y-$ group, where Y may be any of a direct bond, an oxygen atom (O), a sulfur atom (S) or a C_1-C_4 alkylene group. R_6 and R_{14} are independently selected from hydrogen, C_1-C_6 alkyl, aryl and benzyl, or R_6 and R_{14} , when taken together with the carbon to which they are attached, may form a spiro C_3-C_5 cycloalkyl. Thus, compounds
 5 of the invention include compounds of formula (I) where R_6 and R_{14} are hydrogen and Y is a direct bond, such that X may be CH_2 .

Alternatively, X may be an alkenylene moiety, *e.g.*, a *cis*-or *trans*-alkenylene moiety, $C(R_{13})=CH$, where R_{13} may be any of hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl or benzyl. For compounds of formula (I) where X is an
 10 alkenylene moiety, X is preferably a *trans*-alkenylene moiety.

Alternatively, X may be a direct bond. Independent of the selections for A, X and other variables, R_5 is selected from hydrogen, C_1-C_6 alkyl, aryl and benzyl.

Ether side chain component A is generally a hydrophobic moiety. Typically, a hydrophobic moiety is comprised of non-polar chemical groups such as
 15 hydrocarbons or hydrocarbons substituted with halogens or ethers or heterocyclic groups containing nitrogen, oxygen, or sulfur ring atoms. Suitable hydrocarbons are C_5-C_{12} alkyl and C_3-C_{13} carbocyclic rings. Particularly preferred cyclic hydrocarbons include selected aromatic groups such as phenyl, 1-naphthyl, 2-naphthyl, indenyl, acenaphthyl, and fluorenyl and are represented by formulae (III), (IV), (V), (VI), (VII),
 20 or (VIII) respectively.

A suitable "A" group within the compounds of the present invention is a phenyl ring represented by formula (III):



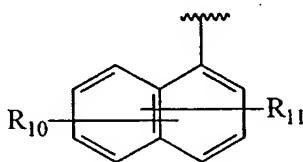
(III)

where R_7 , R_8 and R_9 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl,
 30 trifluoromethyl, C_2-C_7 alkanoyloxy, C_1-C_6 alkyl, C_1-C_6 alkoxy, C_2-C_7 alkoxycarbonyl,

C₁-C₆thioalkyl, aryl and N(R₁₅,R₁₆) where R₁₅ and R₁₆ are independently selected from hydrogen, acetyl, methanesulfonyl, and C₁-C₆alkyl.

For compounds of formula (I) where X is a direct bond or CH₂, at least one of R₇, R₈ and R₉ is preferably selected from amine (-NR₁₅R₁₆, where R₁₅ and R₁₆ are independently hydrogen, acetyl, methanesulfonyl, and C₁-C₆alkyl), bromine, chlorine, fluorine, carboxy, hydroxy, hydroxymethyl, nitro, trifluoromethyl, C₂-C₇alkanoyloxy, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₇alkylcarbonyl, C₁-C₆thioalkyl or aryl groups. For compounds of formula (I) when X is CH=CH, and R₃ and R₄ are hydrogen, at least one of R₇, R₈ and R₉ is preferably a substituent other than hydrogen.

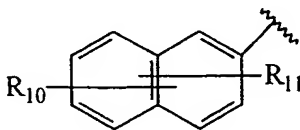
Other suitable "A" groups in compounds of the present invention are 1-naphthyl groups as represented by formula (IV):



(IV)

where R₁₀ and R₁₁ are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C₂-C₇alkanoyloxy, C₁-C₆alkyl, C₁-C₆alkoxy, C₂-C₇alkoxycarbonyl, C₁-C₆thioalkyl, and N(R₁₅,R₁₆) where R₁₅ and R₁₆ are independently selected from hydrogen, acetyl, methanesulfonyl, and C₁-C₆alkyl.

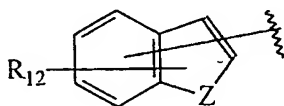
Other suitable "A" groups in compounds of the present invention are 2-naphthyl group as represented by formula (V):



(V)

where R_{10} and R_{11} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are independently selected from
 5 hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl, as defined above.

Other suitable "A" groups in compounds of the present invention are aromatic groups represented by formula (VI):



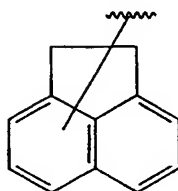
10

(VI)

where R_{12} is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl,
 15 C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl; and Z is selected from CH, CH_2 , O, N and S, where Z may be directly bonded to "X" as shown in formula (I) when Z is CH or N, or Z may be directly bonded to R_{17} when Z is N, and R_{17} is selected from hydrogen, C_1 - C_6 alkyl,
 20 C_3 - C_8 cycloalkyl, aryl and benzyl.

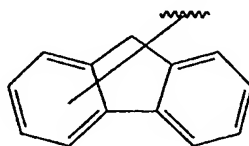
The aryl groups of formula (VI) are derivatives of indene, indole, benzofuran, and thianaphthene when Z is methylene, nitrogen, oxygen, and sulfur, respectively. Preferred heterocyclic groups of formula (VI) include indole where Z is NH, benzofuran where Z is O, and thianaphthene where Z is S. As described below, in
 25 a preferred embodiment, Z is O, S or N- R_{17} , and in a particularly preferred embodiment Z is O or S.

Another suitable "A" group in compounds of the present invention are acenaphthyl groups as represented by formula (VII):



(VII)

Still another suitable "A" group in compounds of the present invention is the fluorenyl group represented by formula (VIII):

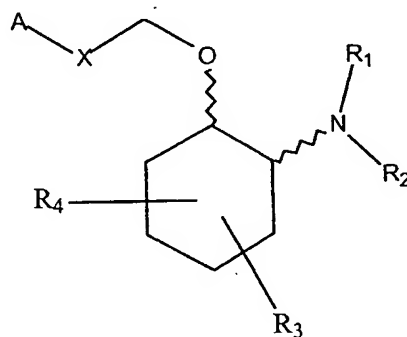


(VIII)

Preferably, ether side chain component A is an acenaphthyl or fluorenyl group only when X is a direct bond or CH_2 . In further preferred embodiments, the acenaphthyl group is a 1-acenaphthyl group, and the fluorenyl group is a 9-fluorenyl group.

As mentioned above, the present invention provides aminocyclohexyl ethers represented by formula (I). In a preferred embodiment X is $(\text{CH}_2)_n\text{-Y}$. For these embodiments, Y is preferably a direct bond, an oxygen atom, or a sulfur atom. In a particularly preferred embodiment, Y is a direct bond or an oxygen atom. In another preferred embodiment Y is a direct bond and X is $\text{C}(\text{R}_6, \text{R}_{14})$, where R_6 and R_{14} are as defined above. In another preferred embodiment, where X is $\text{C}(\text{R}_{13})=\text{CH}$, R_{13} is a hydrogen atom. For these embodiments, R_3 and R_4 are preferably independently attached to the cyclohexane ring at the 4- or 5- positions.

In a preferred embodiment, the invention provides compounds having formula (IX), or a solvate or pharmaceutically acceptable salt thereof:



(IX)

5

wherein, independently at each occurrence,

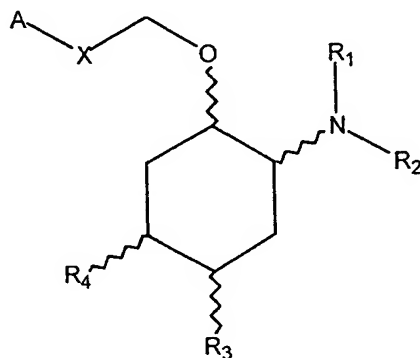
X is selected from a direct bond, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{R}_6, \text{R}_{14})-\text{Y}-$;

Y is selected from a direct bond, O and S; and

R_1 , R_2 , R_3 , R_4 , R_6 , R_7 , R_8 , R_9 , R_{10} , R_{11} , R_{12} , R_{14} , A and Z are defined as

10 above for compounds of formula (I).

In another preferred embodiment, the invention provides a compound having formula (X), or a solvate or pharmaceutically acceptable salt thereof:



(X)

15

wherein, independently at each occurrence,

X is selected from a direct bond, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{R}_6, \text{R}_{14})-\text{Y}-$;

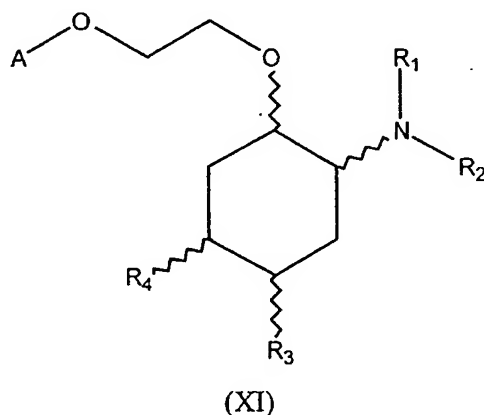
Y is selected from a direct bond, O, and S;

R_1 , R_2 , R_6 and R_{14} are defined as above for compounds of formula (I);

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or
5 5-positions, and are independently selected from hydrogen and $\text{C}_1\text{-C}_6$ alkoxy; and

A is selected from $\text{C}_5\text{-C}_{12}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, and any of formulae
(III), (IV), (V), and (VI) as above for compounds of formula (I), wherein Z, R_7 , R_8 , R_9 ,
 R_{10} , R_{11} and R_{12} are defined as above for compounds of formula (I).

In another preferred embodiment, the invention provides compounds
10 having formula (XI), or a solvate or pharmaceutically acceptable salt thereof:



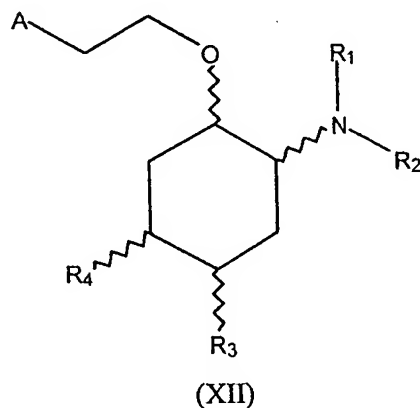
15 wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I);

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or
5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from $\text{C}_5\text{-C}_{12}$ alkyl, $\text{C}_3\text{-C}_8$ cycloalkyl, and any of formulae
20 (III), (IV), (V), and (VI) as above for compounds of formula (I), wherein Z, R_7 , R_8 , R_9 ,
 R_{10} , R_{11} and R_{12} are defined as above for compounds of formula (I).

In another preferred embodiment, the invention provides compounds of formula (XII), or a solvate or pharmaceutically acceptable salt thereof:



5

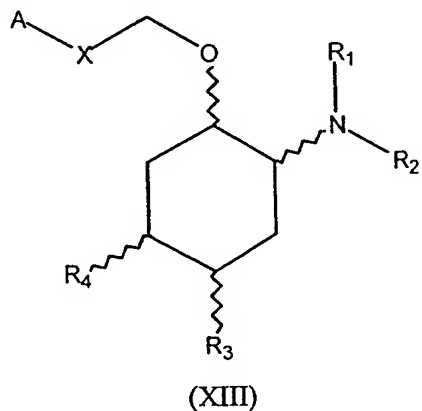
wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I);

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_5 - C_{12} alkyl, C_3 - C_8 cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as above for compounds of formula (I), wherein Z, R_7 , R_8 , R_9 , R_{10} , R_{11} , and R_{12} are defined as above for compounds of formula (I).

In another preferred embodiment, the invention provides compounds of formula (XIII), or a solvate or pharmaceutically acceptable salt thereof:



15

wherein, independently at each occurrence,

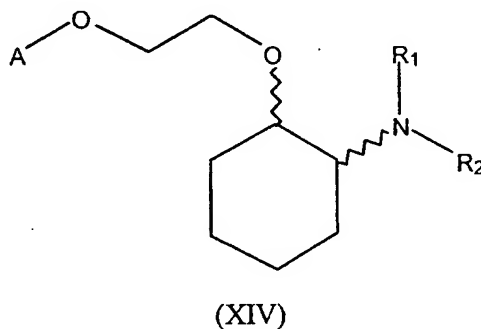
X is selected from a direct bond and $-\text{CH}=\text{CH}-$;

R_1 and R_2 are defined as above for compounds of formula (I);

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or
5 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_3 - C_8 cycloalkyl and any of formulae (III), (IV), (V),
(VI), (VII) and (VIII) as above for compounds of formula (I), where R_8 and R_9 are
defined as above for compounds of formula (I); R_7 , R_{10} , R_{11} and R_{12} are hydrogen, and Z
is selected from O, S and N-R_{17} where R_{17} is selected from hydrogen and methyl; with
10 the proviso that A may be selected from formulae (VII) and (VIII) only when X is a
direct bond.

In another preferred embodiment, the invention provides compounds
having formula (XIV), or a solvate or pharmaceutically acceptable salt thereof:

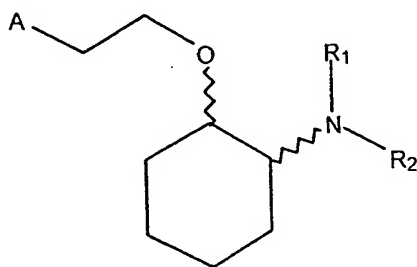


wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I);

20 A is selected from any of formulae (III), (IV), (V) and (VI) as above for
compounds of formula (I), wherein R_7 , R_{10} , R_{11} , and R_{12} , are hydrogen, R_8 and R_9 are
independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine,
methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl,
trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2 , with the proviso that at least
25 one of R_8 and R_9 is not hydrogen; and Z is selected from O and S.

In another preferred embodiment, the invention provides compounds having formula (XV), or a solvate or pharmaceutically acceptable salt thereof:



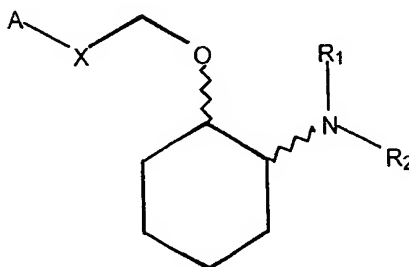
(XV)

wherein, independently at each occurrence,

R_1 and R_2 are defined as above for compounds of formula (I); and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined above for compounds of formula (I), wherein R_7 , R_{10} , R_{11} , and R_{12} , are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2 , with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S.

In another preferred embodiment, the invention provides compounds having formula (XVI), or a solvate or pharmaceutically acceptable salt thereof:



(XVI)

wherein, independently at each occurrence,

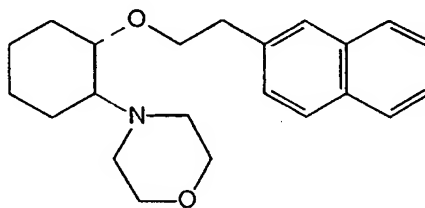
X is selected from a direct bond, *trans*-CH=CH-, -CH₂- and -CH₂-O-;

R_1 and R_2 are both methoxyethyl or, when taken together with the nitrogen atom to which they are attached, complete a ring selected from pyrrolidinyl, ketopyrrolidinyl, acetoxypyrrolidinyl, hydroxypyrrolidinyl, thiazolidinyl, piperidinyl, ketopiperidinyl, acetylpiperazinyl, 1,4-dioxo-7-azaspiro[4.4]non-7-yl, 5 hexahydroazepinyl, morpholinyl, N-methylpiperazinyl and 3-azabicyclo[3.2.2]nonanyl; and

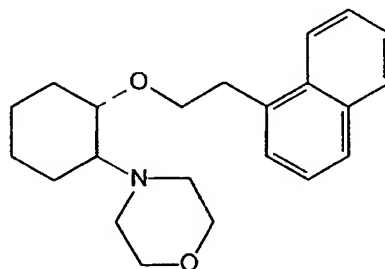
A is selected from cyclohexyl, monochlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 2,4-dibromophenyl, 3-bromophenyl, 4-bromophenyl, 1-naphthyl, 2-naphthyl, 3-benzo(b)thiophenyl, 4-benzo(b)thiophenyl, 10 (2-trifluoromethyl)phenyl, 2,4-di(trifluoromethyl)phenyl, and (4-trifluoromethyl)phenyl.

The following are further preferred compounds of the present invention:

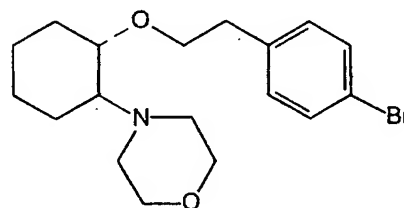
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane



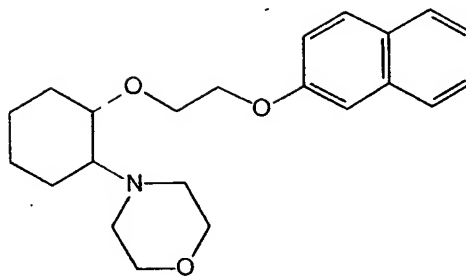
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane



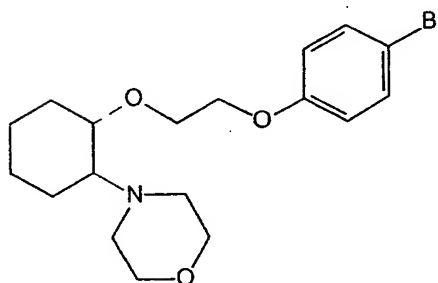
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane



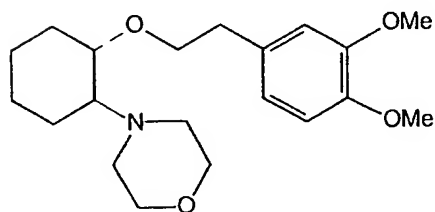
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy]]cyclohexane



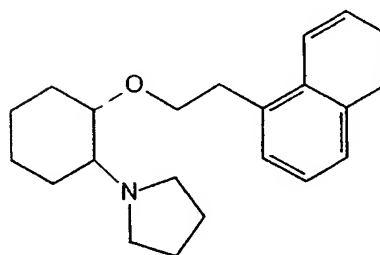
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane



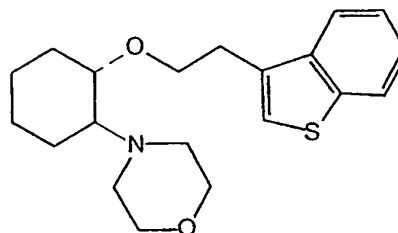
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-[2-(3,4-dimethoxyphenethoxy)]cyclohexane



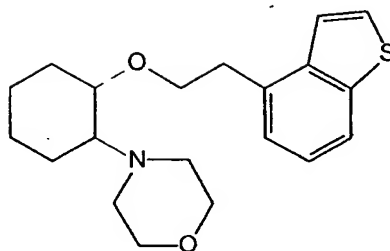
(1R,2R)/(1S,2S)-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane



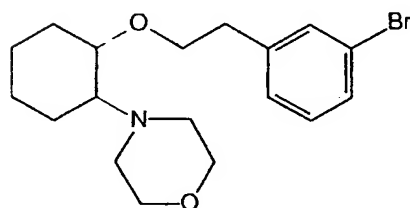
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl))]cyclohexane



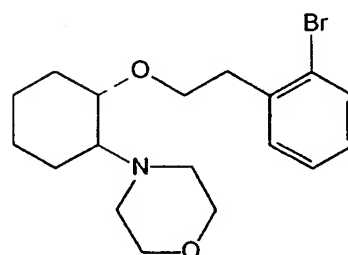
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl))]cyclohexane



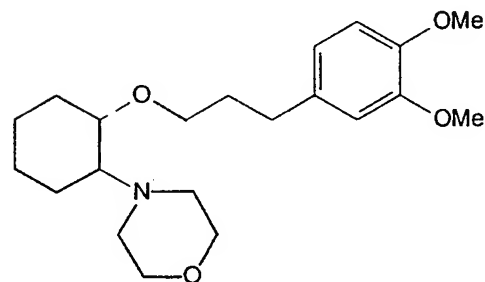
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane



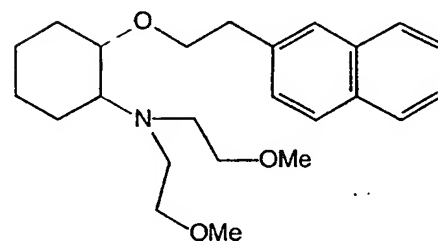
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane



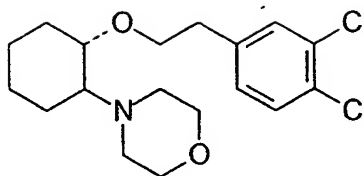
(1R,2R)/(1S,2S)-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)propoxy)]cyclohexane



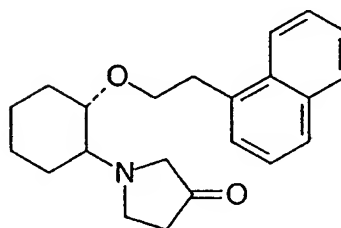
(1R,2R)/(1S,2S)-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane



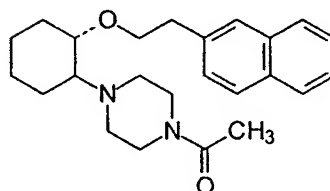
(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-(3,4-dichlorophenoxy)cyclohexane



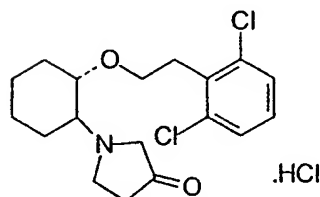
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane



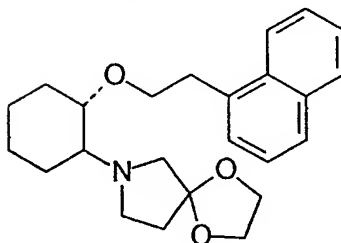
(1R,2R)/(1S,2S)-2-(1-acetylpiperazinyl)-1-(2-naphthenethoxy)cyclohexane



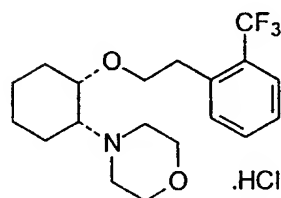
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,6-dichlorophenoxy)cyclohexane



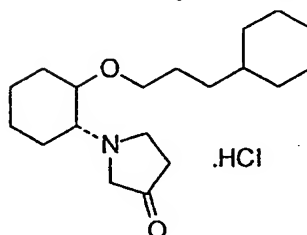
(1R,2R)/(1S,2S)-2-[1,4-dioxo-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane



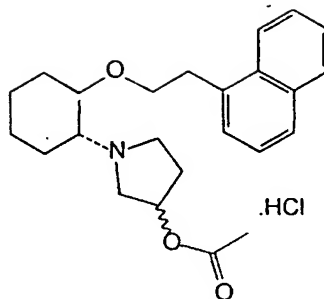
(1R,2S)/(1S,2R)-2-(4-morpholinyl)-1-[(2-trifluoromethyl)phenoxy]cyclohexane monohydrochloride



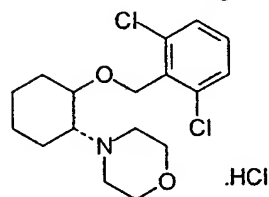
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[3-(cyclohexyl)propoxy]cyclohexane monohydrochloride



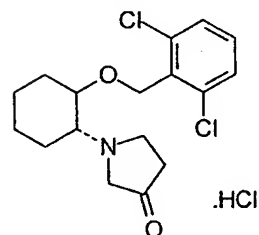
(1R,2R)/(1S,2S)-2-(3-acetoxypyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane
monohydrochloride



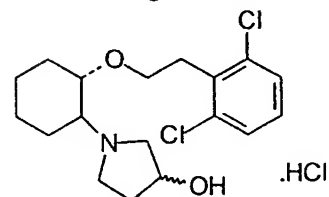
(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane
monohydrochloride



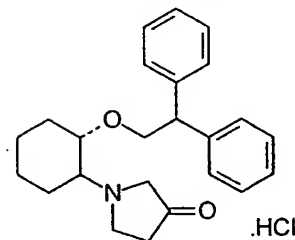
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane
monohydrochloride



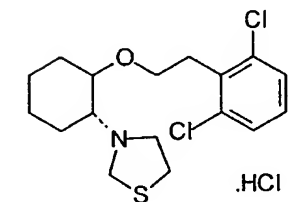
(1R,2R)/(1S,2S)-2-(3-hydroxypyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane
monohydrochloride



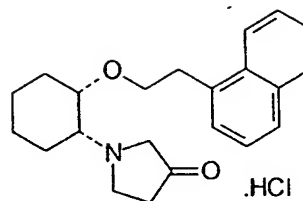
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,2-diphenylethoxy)cyclohexane
monohydrochloride



(1R,2R)/(1S,2S)-2-(3-thiazolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane
monohydrochloride



(1R,2S)/(1S,2R)-2-(3-ketopyrrolidiny)-1-(1-naphthenethoxy)cyclohexane monohydrochloride



Outline of Method of Preparation of Compounds of the Invention

The aminocyclohexyl ether compounds of the present invention contain amino and ether sidechains disposed in a 1,2 arrangement on a cyclohexane ring. Accordingly, the amino and ether sidechains may be disposed in either a *cis* or *trans* relationship, relative to one another and the plane of the cyclohexane ring. The present invention provides synthetic methodology whereby *cis* or *trans* compounds may be prepared.

Trans compounds of the present invention may be prepared in analogy with known synthetic methodology (*see, e.g.*, Shanklin, Jr. et al., U.S. Patent, 5,130,309). Figure 1 outlines the preparation of a *trans* compound of the invention, where this preparation is more fully described in Example 1. As outlined in Figure 1, the preparation of a *trans* compound of the invention may be achieved by following a four step procedure.

In a first step (denoted "i") in Figure 1), cyclohexene epoxide undergoes a ring-opening reaction with an amine. *See, e.g.*, Szmuszkowicz, U.S. Patent 4,145,435. While the reaction can occur at room temperature, typically elevated temperature is preferred in order to drive the reaction to completion in a commercially desirable length of time. The reaction is typically conducted in a solvent, such as water, and the reflux temperature of the solvent provides a suitable temperature. Equal molar amounts of the amine and cyclohexene epoxide typically provide satisfactory results. In any event, the amine nitrogen reacts with the epoxide group to form a 1-hydroxy 2-amino cyclohexane, where the hydroxy and amine groups are typically disposed in a *trans* relationship. A wide variety of amine compounds and substituted cyclohexene oxides may be employed in this general reaction, and Figure 1 illustrates this reaction in the instance where the amine is morpholine and the cyclohexene oxide is unsubstituted.

For other amines or substituted cyclohexene epoxides that may contain other reactive functional groups, appropriate protection groups are introduced prior to step i) being carried out. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

5 In a second step (denoted "ii)" in Figure 1) the hydroxy group that was derived from the epoxide, is converted into an activated form. An "activated form" as used herein means that the hydroxy group is converted into a good leaving group. The leaving group illustrated in Figure 1 is a mesylate group, and that is a preferred leaving group. However, the hydroxy group could be converted into other leaving groups
10 according to procedures well known in the art. In a typical reaction, the aminocyclohexanol compound is treated with methanesulfonyl chloride in the presence of a base, such as triethylamine as shown in Figure 1. The reaction is satisfactorily conducted at about 0°C. An excess of the methanesulfonyl chloride, relative to the aminocyclohexanol, is typically preferred in order to maximally convert the more
15 valuable aminocyclohexanol into the activated form. For some other aminocyclohexanol compounds, it may be necessary to introduce appropriate protection groups prior to step ii) being performed. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

20 In a third step (denoted "iii)" in Figure 1) an alcohol is reacted with a strong base to provide an alkoxide salt. Conversion of an alcohol to an alkoxide (also known as an alcoholate) using strong base is a general reaction, and will work with a wide variety of hydroxy-containing compounds. In some instances, the alcohol compound may have other reactive functional groups that are desirably protected prior
25 to contact of the alcohol with strong base. Suitable protecting groups are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991). Such alcohols are either commercially available or may be obtained by procedures described in the art or adapted therefrom, where suitable procedures may be identified through the Chemical Abstracts and Indices therefor, as
30 developed and published by the American Chemical Society.

In a fourth step (denoted "iv)" in Figure 1), the alcoholate of step "iii)" is reacted with the activated aminocyclohexanol of step "ii)". Thus, generally stated, compounds of the present invention may be prepared by reacting an activated form of the appropriate 1,2-aminocyclohexanol (1 mol) with an alcoholate (1.25 mol) prepared
5 by treatment of the selected alcohol (1.25 mol) with, for example, sodium hydride (1.3 mol). The 1,2-aminocyclohexanol (1 mol) can be activated by forming the corresponding mesylate, in the presence of methanesulfonyl chloride (1.25 mol) and triethylamine (1.5 mol). The mesylate is added quickly to the alcoholate, in a suitable solvent such as dimethylformamide. The reaction temperature is monitored carefully in
10 order to avoid undesired side-reactions such as β -elimination. In general, a reaction temperature of 80-90°C for 2 hours is typically suitable to form compounds of the invention. When the reaction has proceeded to substantial completion, the desired product is recovered from the reaction mixture by conventional organic chemistry techniques, and is purified generally by column chromatography followed by
15 recrystallisation. Protective groups may be removed at the appropriate stage of the reaction sequence. Suitable methods are set forth in, for example, Greene, "Protective Groups in Organic Chemistry", John Wiley & Sons, New York NY (1991).

The reaction sequence described above (and shown in Figure 1) generates the aminocyclohexyl ether as the free base. The pure enantiomeric forms can
20 be obtained by preparative chiral HPLC. The free base may be converted, if desired, to the monohydrochloride salt by known methodologies, and subsequently, if desired, to other acid addition salts by reaction with inorganic or organic salts. Acid addition salts can also be prepared metathetically by reacting one acid addition salt with an acid which is stronger than that of the anion of the initial salt.

25 *Cis* or *trans* compounds of the invention may be prepared according to the chemistry outlined in Figure 2. As shown in Figure 2, 1, 2-aminocyclohexanones may be prepared by Swern oxidation of the corresponding *trans*-1, 2-aminocyclohexanol compounds (which may be prepared as described above) using oxalyl chloride/dimethyl sulfoxide (*see, e.g.*, Synthesis 1980, 165). Subsequent
30 reduction of the aminocyclohexanone with lithium aluminum hydride or sodium

borohydride provides a mixture of *cis*- and *trans*-aminocyclohexanols. The mixture of aminoalcohols may be esterified with an appropriate carboxylic acid by azeotropic distillation in toluene in the presence of a catalytic amount of *p*-toluenesulfonic acid, to provide a diastereomeric mixture of *cis*- and *trans*-esters. The mixture of
5 diastereomeric esters can be separated by preparative chromatography by one of ordinary skill in the art. The racemic *cis*- or *trans* ester preparation could then be reduced with sodium borohydride in the presence of Lewis acid to the corresponding racemic *cis*- or *trans*-ether (see, e.g., *J. Org. Chem.* 25, 875, 1960 and *Tetrahedron* 18, 953, 1962). The racemic *cis*-ether can be resolved by preparative chiral HPLC as
10 discussed above for the *trans*-compound.

Alternatively, *cis* and *trans* compounds of the invention may be prepared according to the chemistry outlined in Figure 3. As shown in Figure 3, cyclohexene oxide can react with an alcohol (ROH) in the presence of $Mg(ClO_4)_2$ (see, e.g., M. Chini et al., *Synlett*, 673-676, 1992) to provide 1,2-hydroxycyclohexyl ethers. Oxidation with
15 pyridinium dichromate (see, e.g., R. Oshima et al., *J. Org. Chem.*, 50, 2613-2621, 1985) yielded the corresponding 1,2-alkoxycyclohexanone. Subsequent reductive amination (R. F. Borch et al., *J. Am. Chem. Soc.*, 93(12), 2897-2904, 1971) provides a mixture of *cis*- and *trans*-aminocyclohexyl ethers. The mixture of diastereomeric ethers can be separated by chromatography by one of ordinary skill in the art. The racemic *cis*- or
20 *trans*-ether so prepared could then be resolved by classical recrystallization methods well known in the art or by preparative chiral HPLC to provide the individual enantiomer: *trans*-(1R,2R), *trans*-(1S,2S), *cis*-(1R,2S) or *cis*-(1S,2R) aminoethers.

The synthetic procedures described herein, especially when taken with the general knowledge in the art, provide sufficient guidance to those of ordinary skill
25 in the art to perform the synthesis, isolation, and purification of the compounds of the present invention.

Compositions and Modes of Administration

In another embodiment, the present invention provides compositions which include a cyclohexylamine compound as described above in admixture or

otherwise in association with one or more inert carriers, excipients and diluents, as well as optional ingredients if desired. These compositions are useful as, for example, assay standards, convenient means of making bulk shipments, or pharmaceutical compositions. An assayable amount of a compound of the invention is an amount
5 which is readily measurable by standard assay procedures and techniques as are well known and appreciated by those skilled in the art. Assayable amounts of a compound of the invention will generally vary from about 0.001 wt% to about 75 wt% of the entire weight of the composition. Inert carriers include any material which does not degrade or otherwise covalently react with a compound of the invention. Examples of suitable
10 inert carriers are water; aqueous buffers, such as those which are generally useful in High Performance Liquid Chromatography (HPLC) analysis; organic solvents such as acetonitrile, ethyl acetate, hexane and the like (which are suitable for use in *in vitro* diagnostics or assays, but typically are not suitable for administration to a warm-blooded animal); and pharmaceutically acceptable carriers, such as physiological saline.

15 Thus, the present invention provides a pharmaceutical or veterinary composition (hereinafter, simply referred to as a pharmaceutical composition) containing a cyclohexylamine compound as described above, in admixture with a pharmaceutically acceptable carrier, excipient or diluent. The invention further provides a pharmaceutical composition containing an effective amount of a
20 cyclohexylamine compound as described above, in association with a pharmaceutically acceptable carrier.

The pharmaceutical compositions of the present invention may be in any form which allows for the composition to be administered to a patient. For example, the composition may be in the form of a solid, liquid or gas (aerosol). Typical routes of
25 administration include, without limitation, oral, topical, parenteral, sublingual, rectal, vaginal, and intranasal. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, epidural, intrasternal injection or infusion techniques. Pharmaceutical composition of the invention are formulated so as to allow the active ingredients contained therein to be bioavailable upon administration of the
30 composition to a patient. Compositions that will be administered to a patient take the

form of one or more dosage units, where for example, a tablet, capsule or cachet may be a single dosage unit, and a container of cyclohexylamine compound in aerosol form may hold a plurality of dosage units.

Materials used in preparing the pharmaceutical compositions should be
5 pharmaceutically pure and non-toxic in the amounts used. The inventive compositions may include one or more compounds (active ingredients) known for a particularly desirable effect. For instance, epinephrine may be combined with an aminocyclohexyl ether compound of the invention, to provide a composition useful to induce local anesthesia. It will be evident to those of ordinary skill in the art that the optimal dosage
10 of the active ingredient(s) in the pharmaceutical composition will depend on a variety of factors. Relevant factors include, without limitation, the type of subject (*e.g.*, human), the particular form of the active ingredient, the manner of administration and the composition employed.

In general, the pharmaceutical composition includes a cyclohexylamine
15 compound as described herein, in admixture with one or more carriers. The carrier(s) may be particulate, so that the compositions are, for example, in tablet or powder form. The carrier(s) may be liquid, with the compositions being, for example, an oral syrup or injectable liquid. In addition, the carrier(s) may be gaseous, so as to provide an aerosol composition useful in, *e.g.*, inhalatory administration.

20 When intended for oral administration, the composition is preferably in either solid or liquid form, where semi-solid, semi-liquid, suspension and gel forms are included within the forms considered herein as either solid or liquid.

As a solid composition for oral administration, the composition may be formulated into a powder, granule, compressed tablet, pill, capsule, cachet, chewing
25 gum, wafer, lozenges, or the like form. Such a solid composition will typically contain one or more inert diluents or edible carriers. In addition, one or more of the following adjuvants may be present: binders such as syrups, acacia, sorbitol, polyvinylpyrrolidone, carboxymethylcellulose, ethyl cellulose, microcrystalline cellulose, gum tragacanth or gelatin, and mixtures thereof; excipients such as starch,
30 lactose or dextrans, disintegrating agents such as alginic acid, sodium alginate,

Primogel, corn starch and the like; lubricants such as magnesium stearate or Sterotex; fillers such as lactose, mannitols, starch, calcium phosphate, sorbitol, methylcellulose, and mixtures thereof; lubricants such as magnesium stearate, high molecular weight polymers such as polyethylene glycol, high molecular weight fatty acids such as stearic acid, silica, wetting agents such as sodium lauryl sulfate, glidants such as colloidal silicon dioxide; sweetening agents such as sucrose or saccharin, a flavoring agent such as peppermint, methyl salicylate or orange flavoring, and a coloring agent.

When the composition is in the form of a capsule, *e.g.*, a gelatin capsule, it may contain, in addition to materials of the above type, a liquid carrier such as polyethylene glycol or a fatty oil.

The composition may be in the form of a liquid, *e.g.*, an elixir, syrup, solution, aqueous or oily emulsion or suspension, or even dry powders which may be reconstituted with water and/or other liquid media prior to use. The liquid may be for oral administration or for delivery by injection, as two examples. When intended for oral administration, preferred compositions contain, in addition to the present compounds, one or more of a sweetening agent, thickening agent, preservative (*e.g.*, alkyl *p*-hydroxybenzoate), dye/colorant and flavor enhancer (flavorant). In a composition intended to be administered by injection, one or more of a surfactant, preservative (*e.g.*, alkyl *p*-hydroxybenzoate), wetting agent, dispersing agent, suspending agent (*e.g.*, sorbitol, glucose, or other sugar syrups), buffer, stabilizer and isotonic agent may be included. The emulsifying agent may be selected from lecithin or sorbitol monooleate.

The liquid pharmaceutical compositions of the invention, whether they be solutions, suspensions or other like form, may include one or more of the following adjuvants: sterile diluents such as water for injection, saline solution, preferably physiological saline, Ringer's solution, isotonic sodium chloride, fixed oils such as synthetic mono or diglycerides which may serve as the solvent or suspending medium, polyethylene glycols, glycerin, propylene glycol or other solvents; antibacterial agents such as benzyl alcohol or methyl paraben; antioxidants such as ascorbic acid or sodium bisulfite; chelating agents such as ethylenediaminetetraacetic acid; buffers such as

acetates, citrates or phosphates and agents for the adjustment of tonicity such as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic. Physiological saline is a preferred adjuvant. An injectable pharmaceutical composition is preferably sterile.

5 A liquid compositions intended for either parenteral or oral administration should contain an amount of the inventive compound such that a suitable dosage will be obtained. Typically, this amount is at least 0.01% of a compound of the invention in the composition. When intended for oral administration, this amount may be varied to be between 0.1 and about 70% of the weight of the composition. Preferred
10 oral compositions contain between about 4% and about 50% of the active cyclohexylamine compound. Preferred compositions and preparations according to the present invention are prepared so that a parenteral dosage unit contains between 0.01 to 10% by weight of active compound.

 The pharmaceutical composition may be intended for topical
15 administration, in which case the carrier may suitably comprise a solution, emulsion, ointment, cream or gel base. The base, for example, may comprise one or more of the following: petrolatum, lanolin, polyethylene glycols, bee wax, mineral oil, diluents such as water and alcohol, and emulsifiers and stabilizers. Thickening agents may be present in a pharmaceutical composition for topical administration. If intended for
20 transdermal administration, the composition may include a transdermal patch or iontophoresis device. Topical formulations may contain a concentration of the inventive compound of from about 0.1 to about 25% w/v (weight per unit volume).

 The composition may be intended for rectal administration, in the form, *e.g.*, of a suppository which will melt in the rectum and release the drug. The
25 composition for rectal administration may contain an oleaginous base as a suitable nonirritating excipient. Such bases include, without limitation, lanolin, cocoa butter and polyethylene glycol. Low-melting waxes are preferred for the preparation of a suppository, where mixtures of fatty acid glycerides and/or cocoa butter are suitable waxes. The waxes may be melted, and the cyclohexylamine compound is dispersed

homogeneously therein by stirring. The molten homogeneous mixture is then poured into convenient sized molds, allowed to cool and thereby solidify.

The composition may include various materials which modify the physical form of a solid or liquid dosage unit. For example, the composition may include materials that form a coating shell around the active ingredients. The materials which form the coating shell are typically inert, and may be selected from, for example, sugar, shellac, and other enteric coating agents. Alternatively, the active ingredients may be encased in a gelatin capsule or cachet.

The composition in solid or liquid form may include an agent which binds to the cyclohexylamine compound and thereby assists in the delivery of the active components. Suitable agents which may act in this capacity include a monoclonal or polyclonal antibody, a protein or a liposome.

The pharmaceutical composition of the present invention may consist of gaseous dosage units, e.g., it may be in the form of an aerosol. The term aerosol is used to denote a variety of systems ranging from those of colloidal nature to systems consisting of pressurized packages. Delivery may be by a liquefied or compressed gas or by a suitable pump system which dispenses the active ingredients. Aerosols of compounds of the invention may be delivered in single phase, bi-phasic, or tri-phasic systems in order to deliver the active ingredient(s). Delivery of the aerosol includes the necessary container, activators, valves, subcontainers, and the like, which together may form a kit. Preferred aerosols may be determined by one skilled in the art, without undue experimentation.

Whether in solid, liquid or gaseous form, the pharmaceutical composition of the present invention may contain one or more known pharmacological agents used in methods for either modulating ion channel activity in a warm-blooded animal or for modulating ion channel activity *in vitro*, or used in the treatment of arrhythmia, diseases of the central nervous system, convulsion, epileptic spasms, depression, anxiety, schizophrenia, Parkinson's disease, respiratory disorders, cystic fibrosis, asthma, cough, inflammation, arthritis, allergies, gastrointestinal disorders, urinary incontinence, irritable bowel syndrome, cardiovascular diseases, cerebral or

myocardial ischemias, hypertension, long-QT syndrome, stroke, migraine, ophthalmic diseases, diabetes mellitus, myopathies, Becker's myotonia, myasthenia gravis, paramyotonia congenita, malignant hyperthermia, hyperkalemic periodic paralysis, Thomsen's myotonia, autoimmune disorders, graft rejection in organ transplantation or
5 bone marrow transplantation, heart failure, hypotension, Alzheimer's disease and other metal disorders, and alopecia. Other agents known to cause libido enhancement, local analgesia or anesthesia may be combined with compounds of the present invention.

The pharmaceutical compositions may be prepared by methodology well known in the pharmaceutical art. The aminocyclohexyl compounds of the invention
10 may be in the form of a solvate in a pharmaceutically acceptable solvent such as water or physiological saline. Alternatively, the compounds may be in the form of the free base or in the form of a pharmaceutically acceptable salt such as the hydrochloride, sulfate, phosphate, citrate, fumarate, methanesulfonate, acetate, tartrate, maleate, lactate, mandelate, salicylate, succinate and other salts known in the art. The appropriate salt
15 would be chosen to enhance bioavailability or stability of the compound for the appropriate mode of employment (*e.g.*, oral or parenteral routes of administration).

A composition intended to be administered by injection can be prepared by combining the cyclohexylamine compound with water, and preferably buffering agents, so as to form a solution. The water is preferably sterile pyrogen-free water. A
20 surfactant may be added to facilitate the formation of a homogeneous solution or suspension. Surfactants are compounds that non-covalently interact with the cyclohexylamine compound so as to facilitate dissolution or homogeneous suspension of the cyclohexylamine compound in the aqueous delivery system. Surfactants are desirably present in aqueous compositions of the invention because the
25 cyclohexylamine compounds of the present invention are typically hydrophobic. Other carriers for injection include, without limitation, sterile peroxide-free ethyl oleate, dehydrated alcohols, propylene glycol, as well as mixtures thereof.

Suitable pharmaceutical adjuvants for the injecting solutions include stabilizing agents, solubilizing agents, buffers, and viscosity regulators. Examples of
30 these adjuvants include ethanol, ethylenediaminetetraacetic acid (EDTA), tartrate

buffers, citrate buffers, and high molecular weight polyethylene oxide viscosity regulators. These pharmaceutical formulations may be injected intramuscularly, epidurally, intraperitoneally, or intravenously.

Pharmacological Testing

5 As noted above, the present invention provides for utilizing the compounds described above in *in vitro* and *in vivo* methods. In one embodiment, ion channels, such as cardiac sodium channels, are blocked *in vitro* or *in vivo*.

 Ion channels are ubiquitous membrane proteins in the cells of warm-blooded animals such as mammals. Their critical physiological roles include control of
10 the electrical potential across the membrane, mediation of ionic and fluid balance, facilitation of neuromuscular and neuronal transmission, rapid transmembrane signal transduction, and regulation of secretion and contractility.

 Accordingly, compounds that are capable of modulating the activity or function of the appropriate ion channels will be useful in treating or preventing a variety
15 of diseases or disorders caused by defective or inadequate function of the ion channels. The compounds of the invention are found to have significant activity in modulating ion channel activity both *in vivo* and *in vitro*.

 Thus, the present invention provides for methods of treating a disease or condition in a warm-blooded animal suffering from or having the disease or condition,
20 and/or preventing a disease or condition from arising in a warm-blooded animal, wherein a therapeutically effective amount of a compound of formula (I), or a composition containing a compound of formula (I) is administered to a warm-blooded animal in need thereof. The diseases and conditions to which the compounds, compositions and methods of the present invention may be applied as follows:
25 arrhythmia, diseases of the central nervous system, convulsion, epileptic spasms, depression, anxiety, schizophrenia, Parkinson's disease, respiratory disorders, cystic fibrosis, asthma, cough, inflammation, arthritis, allergies, gastrointestinal disorders, urinary incontinence, irritable bowel syndrome, cardiovascular diseases, cerebral or myocardial ischemias, hypertension, long-QT syndrome, stroke, migraine, ophthalmic

diseases, diabetes mellitus, myopathies, Becker's myotonia, myasthenia gravis, paramyotonia congenita, malignant hyperthermia, hyperkalemic periodic paralysis, Thomsen's myotonia, autoimmune disorders, graft rejection in organ transplantation or bone marrow transplantation, heart failure, hypotension, Alzheimer's disease or other
5 mental disorder, and alopecia.

Furthermore, the present invention provides a method for producing local analgesia or anesthesia in a warm-blooded animal which includes administering to a warm-blooded animal in need thereof an effective amount of a compound of formula (I) or a pharmaceutical composition containing a compound of formula (I). These
10 methods may be used to relieve or forestall the sensation of pain in a warm-blooded animal.

Furthermore, the present invention provides a method wherein a preparation that contains ion channels is contacted with, or a warm-blooded animal (e.g., a mammal, such as a human) is administered an effective amount of an
15 aminocyclohexyl ether compound of the invention. Suitable preparations containing cardiac sodium channels include cells isolated from cardiac tissue as well as cultured cell lines. The step of contacting includes, for example, incubation of ion channels with a compound under conditions and for a time sufficient to permit modulation of the activity of the channels by the compound.

20 In another embodiment, the compounds described above are provided for treating arrhythmia. As used herein, "treating arrhythmia" refers to both therapy for arrhythmia and for the prevention of arrhythmias occurring in a heart that is susceptible to arrhythmia. An effective amount of a composition of the present invention is used to treat arrhythmia in a warm-blooded animal, such as a human. Methods of administering
25 effective amounts of antiarrhythmic agents are well known in the art and include the administration of an oral or parenteral dosage form. Such dosage forms include, but are not limited to, parenteral dosage form. Such dosage forms include, but are not limited to, parenteral solutions, tablets, capsules, sustained release implants, and transdermal delivery systems. Generally, oral or intravenous administration is preferred. The
30 dosage amount and frequency are selected to create an effective level of the agent

without harmful effects. It will generally range from a dosage of from about 0.1 to about 100 mg/kg/day, and typically from about 0.1 to 10 mg/kg where administered orally or intravenously for antiarrhythmic effect.

Administration of compositions of the present invention may be carried out in combination with the administration of other agents. For example, it may be desired to administer an opioid antagonist, such as naloxone, if a compound exhibits opioid activity where such activity may not be desired. The naloxone may antagonize opioid activity of the administered compound without adverse interference with the antiarrhythmic activity. As another example, an aminocyclohexyl ether compound of the invention may be co-administered with epinephrine in order to include local anesthesia.

In order to assess whether a compound has a desired pharmacological activity with the present invention, it is subjected to a series of tests. The precise test to employ will depend on the physiological response of interest. The published literature contains numerous protocols for testing the efficacy of a potential therapeutic agent, and these protocols may be employed with the present compounds and compositions.

For example, in connection with treatment or prevention of arrhythmia, a series of four tests may be conducted. In the first of these tests, a compound of the present invention is given as increasing (doubling with each dose) intravenous boluses every 8 minutes to a pentobarbital anesthetized rat. The effects of the compound on blood pressure, heart rate and the ECG are measured 30 seconds, 1, 2, 4 and 8 minutes after each dose. Increasing doses are given until the animal dies. The cause of death is identified as being of either respiratory or cardiac origin. This test gives an indication as to whether the compound is modulating the activity of sodium channels and/or potassium channels, and in addition gives information about acute toxicity. The indices of sodium channel blockade are increasing P-R interval and QRS widening of the ECG. Potassium channel blockade results in Q-T interval prolongation of the ECG.

A second test involves administration of a compound as an infusion to pentobarbital anesthetized rats in which the left ventricle is subjected to electrical square wave stimulation performed according to a preset protocol described in further

detail below. This protocol includes the determination of thresholds for induction of extrasystoles and ventricular fibrillation. In addition, effects on electrical refractoriness are assessed by a single extra beat technique. In addition effects on blood pressure, heart rate and the ECG are recorded. In this test, sodium channel blockers produce the
5 ECG changes expected from the first test. In addition, sodium channel blockers also raise the thresholds for induction of extrasystoles and ventricular fibrillation. Potassium channel blockade is revealed by increasing refractoriness and widening of the Q-T intervals of the ECG.

A third test involves exposing isolated rat hearts to increasing
10 concentrations of a compound. Ventricular pressures, heart rate, conduction velocity and ECG are recorded in the isolated heart in the presence of varying concentrations of the compound. The test provides evidence for direct toxic effects on the myocardium. Additionally, selectivity, potency and efficacy of action of a compound can be ascertained under conditions simulating ischemia. Concentrations found to be effective
15 in this test are expected to be efficacious in the electrophysiological studies.

A fourth test is estimation of the antiarrhythmic activity of a compound against the arrhythmias induced by coronary artery occlusion in anaesthetized rats. It is expected that a good antiarrhythmic compound will have antiarrhythmic activity at doses which have minimal effects on either the ECG, blood pressure or heart rate under
20 normal conditions.

All of the foregoing tests are performed using rat tissue. In order to ensure that a compound is not having effects which are only specific to rat tissue, further experiments are performed in dogs and primates. In order to assess possible sodium channel and potassium channel blocking action *in vivo* in dogs, a compound is
25 tested for effects on the ECG, ventricular epicardial conduction velocity and responses to electrical stimulation. An anesthetized dog is subjected to an open chest procedure to expose the left ventricular epicardium. After the pericardium is removed from the heart a recording/stimulation electrode is sewn onto the epicardial surface of the left ventricle. Using this array, and suitable stimulation protocols, conduction velocity across the
30 epicardium as well as responsiveness to electrical stimulation can be assessed. This

information coupled with measurements of the ECG allows one to assess whether sodium and/or potassium channel blockade occurs. As in the first test in rats, a compound is given as a series of increasing bolus doses. At the same time possible toxic effects of a compound on the dog's cardiovascular system is assessed.

- 5 The effects of a compound on the ECG and responses to electrical stimulation are also assessed in intact, halothane anesthetized baboons (*Papio anubis*). In this preparation, a blood pressure cannula and ECG electrodes are suitably placed in an anesthetized baboon. In addition, a stimulating electrode is placed into the right ventricle, together with a monophasic action potential electrode. As in the tests
10 described above, ECG and electrical stimulation response to a compound reveal the possible presence of sodium and/or potassium channel blockade. The monophasic action potential also reveals whether a compound widens the action potential, an action expected of a potassium channel blocker.

- As another example, in connection with the mitigation or prevention of
15 the sensation of pain, the following test may be performed. To determine the effects of a compound of the present invention on an animal's response to a sharp pain sensation, the effects of a slight prick from a 7.5 g weighted syringe fitted with a 23G needle as applied to the shaved back of a guinea pig (*Cavia porcellus*) is assessed following subcutaneous administration of sufficient (50 µl, 10 mg/ml) solution in saline to raise a
20 visible bleb on the skin. Each test was done on the central area of the bleb and also on its periphery to check for diffusion of the test solution from the point of administration. If the test animal produces a flinch in response to the stimulus, this demonstrates the absence of blockade of pain sensation. Testing was carried out at intervals for up to 4 hours post administration. The sites of bleb formation were examined after 24 hours
25 and showed no skin abnormalities consequent to local administration of test substances or of saline, the vehicle used for preparation of the test solutions.

Other Compositions

The present invention also provides kits that contain a pharmaceutical composition which includes one or more compounds of the above formulae. The kit

also includes instructions for the use of the pharmaceutical composition for modulating the activity of ion channels, for the treatment of arrhythmia or for the production of local analgesia and/or anesthesia, and for the other utilities disclosed herein. Preferably, a commercial package will contain one or more unit doses of the pharmaceutical composition. For example, such a unit dose may be an amount sufficient for the preparation of an intravenous injection. It will be evident to those of ordinary skill in the art that compounds which are light and/or air sensitive may require special packaging and/or formulation. For example, packaging may be used which is opaque to light, and/or sealed from contact with ambient air, and/or formulated with suitable coatings or excipients.

The following examples are offered by way of illustration and not by way of limitation. In the Examples, and unless otherwise specified, starting materials were obtained from well-known commercial supply houses, *e.g.*, Aldrich Chemical Company (Milwaukee, WI), and were of standard grade and purity. "Ether" and "ethyl ether" each refers to diethyl ether; "h." refers to hours; "min." refers to minutes; "GC" refers to gas chromatography; "v/v" refers to volume per volume; and ratios are weight ratios unless otherwise indicated.

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EXAMPLES

EXAMPLE 1

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(2-NAPHTHENETHOXY)]CYCLOHEXANE

MONOHYDROCHLORIDE

25

(COMPOUND #1)

(i) Morpholine (5 mL, 57 mmol), cyclohexene oxide (5.8 mL, 57 mmol) and water (3 mL) were refluxed for 1.5h. GC analysis showed the reaction to be complete. The cooled mixture was partitioned between saturated NaOH solution (50 mL) and ether (75 mL). The aqueous layer was backwashed with ether (30 mL) and the combined ether layers were dried over sodium sulfate. The ether was removed *in vacuo* to leave a yellow oil (9.83 g). The crude product, (±)-*trans*-[2-(4-

morpholinyl)]cyclohexanol, was purified by vacuum distillation (b.p. 75-80°C at full vacuum) to give a clear liquid (8.7 g). Yield 82.5%.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (6.0 g, 32.4 mmol) and triethylamine (6.8 mL, 48 mmol) in 5 dichloromethane (100 mL) was added via cannula a solution of methanesulfonyl chloride (3.10 mL, 40 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 10 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 8.5 g (100% yield) of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion previously washed with hexanes (3 x 20 mL), (1.24 g, 51.6 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-naphthenethanol (6.8 g, 40 mmol) in dry 15 dimethylformamide (50 mL). Addition was followed by gas evolution and, as the reaction mixture was stirred at room temperature, it began to gel. The mesylate as prepared in (ii) above was dissolved in dimethylformamide (50 mL) and the resulting solution was added quickly via cannula to the slurry of alcoholate. The reaction mixture was heated to 80°C and then the temperature reduced to 40°C. The resulting 20 yellow solution was poured into ice-water (1500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (500 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 13.4 g of an amber oil which was dissolved in water (150 mL) and the pH of the solution was adjusted to pH 2 with aqueous 1M HCl. The acidic 25 aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 7.16 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with 30 a mixture of ethyl acetate-chloroform (1:1, v/v) as eluent to yield 4.37 g of the pure free

base. The product was dissolved in ethyl ether (80 mL) and converted to the monohydrochloride salt by adding saturated solution of HCl in ethyl ether (80 mL). An oil came out of the solution, the solvent was evaporated *in vacuo* and the residue dissolved in the minimum amount of warm ethyl alcohol, addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 3.83 g (31% yield) of the title compound, m.p. 158-160°C, having the elemental analysis indicated in Table 1.

EXAMPLE 2

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(1-NAPHTHENETHOXY)]CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #2)

- (i) The starting *trans*-aminocyclohexanol is prepared according to example 1.
- (ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (6.0 g, 32 mmol) and triethylamine (6.8 mL, 48 mmol) in dichloromethane (100 mL) was added via cannula a solution of methanesulfonyl chloride (3.10 mL, 40 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 9.0 g of the crude mesylate.
- (iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 20 mL) (1.30 g, 51.6 mmol), in dry dimethylformamide (50 mL) was added via cannula a solution of 1-naphthenethanol (6.8 g, 40 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of gas and the reaction mixture was stirred at room temperature for 4 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the slurry of alcoholate. The

reaction mixture was heated to 80°C for 3 hours, then the temperature was reduced to 35°C for overnight stirring. The reaction mixture was poured into ice-water (1500 mL) and extracted with ethyl acetate (3 x 300 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (500 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 12.0 g of an oil which was dissolved in ether (80 mL) and treated with a saturated solution of HCl in ether. A sticky product came out of solution, the solvent was evaporated *in vacuo* and the resulting crude hydrochloride salt was dissolved in water (200 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 7.20 g of the crude free amino ether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (80 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (80 mL). A white product precipitated and this solid was collected and dissolved in the minimum amount of warm ethyl alcohol; addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 2.30 g of the title compound, m.p. 198-200°C, having the elemental analysis indicated in Table 1.

EXAMPLE 3

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(4-BROMOPHENETHOXY)]CYCLOHEXANE

MONOHYDROCHLORIDE

(COMPOUND #3)

25

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-morpholinyl]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (25 mL) was added via cannula a solution of

30

methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (25 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 2 hours. The reaction mixture was diluted with dichloromethane (50 mL) and washed with water (2 x 50 mL) and the combined
5 aqueous washings back extracted with dichloromethane (25 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.7 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.62 g, 25.8 mmol) in dry dimethylformamide (25 mL) was
10 added via cannula a solution of 4-bromophenethylalcohol (4.0 g, 20 mmol) in dimethylformamide (50 mL). Addition was followed by evolution of gas and the reaction mixture was stirred at room temperature for 4 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the slurry of alcoholate. The
15 reaction mixture was heated to 80°C for 2 hours, then the temperature was reduced to 35°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (150 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.4 g of an oil
20 which was dissolved in ether (80 mL) was treated with a saturated solution of HCl in ether. An oil came out of solution, the solvent was evaporated *in vacuo* and the residue was dissolved in water (100 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 50 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 50 mL), the
25 combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.67 g of the crude free amino ether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (30 mL) and converted to the monohydrochloride salt by
30 adding a saturated solution of HCl in ethyl ether (30 mL). The solvent was evaporated

and the residue dissolved in the minimum amount of ethyl alcohol, addition of a large volume of ethyl ether triggered crystallization. The crystals were collected to afford 1.31 g of the title compound, m.p. 148-151°C, having the elemental analysis indicated in Table 1.

5

EXAMPLE 4

(±)-TRANS-[2-(4-MORPHOLINYL)-1-[2-(2-NAPHTHOXY)ETHOXY]]CYCLOHEXANE

MONOHYDROCHLORIDE

(COMPOUND #4)

10 (i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride
15 (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in*
20 *vacuo* to provide 4.3 g (100% yield) of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.7 g, 29 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-(2-naphthoxy)ethanol (3.76 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of gas and the
25 reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The resulting reaction mixture was heated overnight to 90°C and then cooled to room temperature. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl
30 acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated

aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.8 g of a yellow oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). The resulting precipitate was collected, partially solubilized in water (200 mL) and the
5 heterogeneous aqueous solution was extracted with ether (2 x 100 mL). The remaining insoluble material was collected and recrystallized in boiling ethanol (75 mL) to provide a first crop of the desired product. The acidic aqueous solution was basified to pH 10 with aqueous 50% NaOH and extracted with ether (2 x 50 mL). The combined organic
10 extracts were dried over sodium sulfate and concentrated *in vacuo* to provide 1.6 g of the crude free amino ether. The product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl acetate-dichloromethane as eluent to yield 0.73 g of a pale yellow oil. The pure free base was then dissolved in ether (50 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ether
15 (50 mL). The white precipitate was collected and recrystallized in boiling ethanol (40 mL) to provide a second crop. Combination of the two crops afforded 1.03 g of the title compound, m.p. 235-237°C, having the elemental analysis indicated in Table 1.

EXAMPLE 5

(±)-TRANS-[2-(4-MORPHOLINYL)-1-[2-(4-BROMOPHENOXY)ETHOXY]]CYCLOHEXANE

20

MONOHYDROCHLORIDE

(COMPOUND #5)

(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in
25 dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50
30 mL) and the combined aqueous washings back extracted with dichloromethane (50

mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 3.95 g (92% yield) of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.63 g, 26 mmol) in dry dimethylformamide (50 mL) was added
5 via cannula a solution of 2-(4-bromophenoxy)ethanol (4.34 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction
10 mixture was heated to 90°C for 90 min. and then the temperature was reduced to 40°C and the reaction was stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution (300 mL) of sodium chloride and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.35 g of a
15 yellow oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). The resulting white solid was collected and recrystallized in boiling ethanol (150 mL) to yield 3.7 g (54% yield) of the pure title compound, m.p. 228-230°C, having the elemental analysis indicated in Table 1.

20

EXAMPLE 6

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(3,4-DIMETHOXYPHENETHOXY)]CYCLOHEXANE

MONOHYDROCHLORIDE

(COMPOUND #6)

(i) The starting *trans*-aminocyclohexanol is prepared according to
25 example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10
30 min., the reaction mixture was stirred for another hour at 0°C and then at room

temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.18 g of the crude mesylate.

- 5 (iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.64 g, 27 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 3,4-dimethoxyphenethyl alcohol (3.64 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared
- 10 in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 80°C for 90 min. and then the temperature was reduced to 40°C and stirring continued overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts
- 15 were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.18 g of the crude product which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). The solvent was evaporated *in vacuo* and the residual oil was taken up with water (100 mL) and extracted with ether (2x50 mL). The
- 20 aqueous layer was basified to pH10 with 50% NaOH aqueous solution and extracted with ether (2x50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl acetate and dichloromethane (1:1, v/v) as eluent to provide 2.8 g of a pale yellow oil. The free base was dissolved in ether (80
- 25 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ether (80 mL). The sticky precipitate was collected, dissolved in the minimum amount of ethanol and a large excess of ether was added to trigger crystallization of 2.24 g (36% yield) of the title compound, m.p. 148-150°C, having the elemental analysis indicated in Table 1.

EXAMPLE 7

(±)-TRANS-[2-(1-PYRROLIDINYL)-1-(1-NAPHTHENETHOXY)]CYCLOHEXANE

MONOHYDROCHLORIDE

(COMPOUND #7)

- 5 (i) Pyrrolidine (25 mL, 300 mmol), cyclohexene oxide (30 mL, 297 mmol) and water (10 mL) were refluxed for 3 h. GC analysis showed the reaction to be complete. The cooled mixture was partitioned between saturated NaOH solution (10 mL) and ether (150 mL). The aqueous layer was backwashed with ether (2x100 mL) and the combined ether layers were dried over sodium sulfate. The ether was removed
10 *in vacuo* to leave a yellow oil. The crude product was purified by vacuum distillation (b.p. 66-69°C at full vacuum) to give a clear liquid (43.9 g). Yield 87%.
- (ii) To a chilled (0°C) solution of (±)-*trans*-[2-(pyrrolidinyl)]cyclohexanol (2.74 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of
15 methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 3.24 g of the crude mesylate.
- 20 (iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 ml), (0.64 g, 27 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 1-naphthenethanol (3.64 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared
25 in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 80°C for 90 min. and then its temperature was reduced to 40°C and it was stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were
30 backwashed with a saturated aqueous solution with sodium chloride (300 mL) and dried

over sodium sulfate. Evaporation of the solvent *in vacuo* provided 9.00 g of the crude product which was dissolved in ether (50 mL) and treated with a saturated solution of HCl in ether (50 mL). The solvent was evaporated *in vacuo* and the residual oil was taken up with water (100 mL) and extracted with ether (2x50 mL). The aqueous layer
5 was basified to pH10 with 50% NaOH aqueous solution and extracted with ether (2x50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl methanol and chloroform (2:8, v/v) as eluent. The free amino ether was partially dissolved in ether (80 mL), insoluble materials were filtered
10 off, and then a saturated solution of HCl in ether (80 mL) was added to the filtrate. The solvent was evaporated *in vacuo*, the residue was dissolved in acetone and addition of aliquots of ether triggered slow crystallization. 2 crops of the title compound (0.88 g), m.p. 103-105°C were collected, having the elemental analysis indicated in Table 1.

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EXAMPLE 8

(±)-TRANS-[2-(4-

MORPHOLINYL)-1-(2-(BENZO[B]THIOPHEN-3-YL)ETHOXY)]CYCLOHEXANE

MONOHYDROCHLORIDE

(COMPOUND #8)

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(i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride
25 (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 3 hours. The reaction mixture was washed with water (3 x 30 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to
30 provide 5.25 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.60 g, 25 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-(benzo[b]thiophen-3yl)ethanol (3.56 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of gas and the
5 reaction mixture was stirred at room temperature for 3 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (2 min.) via cannula to the reaction mixture. The reaction mixture was heated to 75°C for 2 hours, then the temperature was reduced to 65°C and stirring continued overnight. The reaction mixture was poured into ice-water (800 mL)
10 and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution (300 mL) of sodium chloride and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 7.7 g of an oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). An oil precipitated from the solution, the solvent was evaporated *in vacuo*
15 and the resulting crude hydrochloride salt was dissolved in water (200 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with aqueous 50% sodium hydroxide. The basic aqueous solution was extracted with ethyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.30 g of the crude free aminoether. The crude
20 product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate and dichloromethane (1:1, v/v) as eluent to provide the free base. The product was dissolved in ethyl ether (100 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (100 mL). The solvent was evaporated *in vacuo* and the residue was dissolved in the minimum amount of boiling
25 methanol to provide a first crop (0.7 g) of crystalline product on cooling. Addition of diethyl ether to the methanol filtrate provided a second crop (0.55 g). The two crops were combined to yield 1.25 g of the title compound, m.p. 158-160°C, having the elemental analysis indicated in Table 1.

EXAMPLE 9

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(2-(BENZO[B]THIOPHEN-4-YL)ETHOXY)]

CYCLOHEXANE MONOHYDROCHLORIDE

(COMPOUND #9)

5 (i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24.0 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 3 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.24 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.60 g, 25 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-(benzo[b]thiophen-4-yl)ethanol (3.56 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 3 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (2 min.) via cannula to the reaction mixture. The reaction mixture was heated to 85°C for 2 hours, then the temperature was reduced to 40°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution (300 mL) of sodium chloride and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.2 g of an oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). An oil precipitated and the solvent was evaporated *in vacuo* and the resulting crude hydrochloride salt was dissolved in water (200 mL). The acidic aqueous solution

was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with an aqueous solution of sodium hydroxide (50% w/v). The basic aqueous solution was extracted with ethyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.0 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (50 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ethyl ether (50 mL). The solvent was evaporated *in vacuo*, the residue was dissolved in the minimum amount of cold ethanol and addition of ether triggered formation of crystals (1.17 g), m.p. 178-180°C, having the elemental analysis indicated in Table 1.

EXAMPLE 10

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(3-BROMOPHENETHOXY)]CYCLOHEXANE

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MONOHYDROCHLORIDE

(COMPOUND #10)

- (i) The starting *trans*-aminocyclohexanol is prepared according to example 1.
- (ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 3 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 5.4 g of the crude mesylate.
- (iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.60 g, 25 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 3-bromophenethyl alcohol (4.0 g, 20 mmol) in dry

dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 3 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (2 min.) via cannula to the reaction mixture. The reaction mixture was heated to 85°C for 2 hours, then the temperature was reduced to 45°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.0 g of an oil which was dissolved in ether (100 mL) and treated with a saturated solution of HCl in ether (100 mL). An oil precipitated and the solvent was evaporated *in vacuo* and the resulting crude hydrochloride salt was dissolved in water (200 mL). The acidic aqueous solution was extracted with ethyl ether (2 x 100 mL) and then basified to pH 10 with an aqueous solution of sodium hydroxide (50% w/v). The basic aqueous solution was extracted with ethyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 2.9 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (50 mL) and converted to the monohydrochloride salt by adding saturated solution of HCl in ethyl ether (50 mL). The solvent was evaporated *in vacuo*, the residue was dissolved in the minimum amount of cold ethanol and addition of ether triggered formation of crystals (0.53 g), m.p. 145-148°C, having the elemental analysis indicated in Table 1.

EXAMPLE 11

(±)-TRANS-[2-(4-MORPHOLINYL)-1-(2-BROMOPHENETHOXY)]CYCLOHEXANE

MONOHYDROCHLORIDE

(COMPOUND #11)

5 (i) The starting *trans*-aminocyclohexanol is prepared according to example 1.

(ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24.0 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 3 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 5.9 g of the crude mesylate.

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(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.60 g, 25 mmol) in dry dimethylformamide (50 mL) was added via cannula a solution of 2-bromophenethyl alcohol (4.0 g, 20 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 3 hours. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (2 min.) via cannula to the reaction mixture. The reaction mixture was heated to 85°C for 2 hours, then the temperature was reduced to 45°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.4 g of an oil which was dissolved in 1.0 M HCl aqueous solution (50 mL), the volume was adjusted to 200 mL with water and the pH adjusted to pH 2 with 1.0 M HCl aqueous solution. The acidic aqueous solution was extracted with ethyl ether (3 x 100 mL) and then basified to

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pH 10 with 50% aqueous sodium hydroxide solution. The basic aqueous solution was extracted with ethyl ether (3 x 100 mL), the combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 2.8 g of the crude free aminoether. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) with
5 a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent to provide the pure free base. The product was dissolved in ethyl ether (50 mL) and converted to the monohydrochloride salt by adding saturated solution of HCl in ethyl ether (50 mL). The solvent was evaporated *in vacuo*, the residue was dissolved in the minimum amount of cold ethanol and addition of ether triggered formation of crystals which were
10 collected in two crops (0.74 g), m.p. 140-142°C, having the elemental analysis indicated in Table 1.

EXAMPLE 12

(±)-TRANS-[2-(4-

15 MORPHOLINYL)-1-(3-(3,4-DIMETHOXYPHENYL)-1-PROPOXY)]CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #12)

- (i) The starting *trans*-aminocyclohexanol is prepared according to example 1.
- 20 (ii) To a chilled (0°C) solution of (±)-*trans*-[2-(4-morpholinyl)]cyclohexanol (3.0 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.0 mmol) in dichloromethane (50 mL). The addition was completed in 10 min., the reaction mixture was stirred for another hour at 0°C and then at room
25 temperature for 4 hours. The dichloromethane mixture was washed with water (2 x 50 mL) and the combined aqueous washings back extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide the crude mesylate.
- (iii) To sodium hydride, 80% oil dispersion, previously washed with
30 hexanes (3 x 10 mL), (0.6 g, 27 mmol) in dry dimethylformamide (50 mL) was added

via cannula a solution of 3-(3,4-dimethoxyphenyl)-1-propanol (3.93 g, 20.0 mmol) in dry dimethylformamide (50 mL). Addition was followed by evolution of a gas and the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated to 90°C for 90 min. and then the temperature was reduced to 45°C and stirring continued overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a saturated aqueous solution of sodium chloride (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.5 g of the crude product which was dissolved in 15% HCl aqueous solution (200 mL) and extracted with ether (2x100 mL). The aqueous layer was basified to pH10 with 50% NaOH aqueous solution and extracted with ether (2x100 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo*. The crude product was purified by chromatography on silica gel 60 (70-230 mesh) using a mixture of ethyl acetate and dichloromethane (1:1, v/v) as eluent to provide the free base which was dissolved in ether (80 mL) and converted to the monohydrochloride salt by adding a saturated solution of HCl in ether (80 mL). The sticky precipitate was collected, dissolved in the minimum amount of warm ethanol and a large excess of ether was added to trigger crystallization of the title compound, m.p. 175-177°C, having the elemental analysis indicated in Table 1.

EXAMPLE 13

(±)-TRANS-[2-[BIS(2 METHOXYETHYL)AMINO]-1-(2-NAPHTHENETHOXY)]CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #13)

(i) Bis-(2-methoxyethyl)amine(25 mL, 169 mmol) and cyclohexene oxide (17.2 mL, 170 mmol) were mixed in water (5 mL) and the resulting mixture was refluxed for 30 hours. The cooled reaction mixture was partitioned between 10%

NaOH aqueous (200 mL) and diethyl ether (200 mL). The aqueous layer was extracted twice more with diethyl ether (2 x 100 mL), the combined organic layers were washed with water (8 mL) and dried over sodium sulfate. The solvent was evaporated *in vacuo* to provide the crude product which was vacuum distilled to provide 26.4 g of pure colorless oil.

(ii) To a chilled (0°C) solution of (±)-*trans*-2-[bis(2-methoxyethyl)amino]cyclohexanol) 4.63 g, 20.00 mmol) and triethylamine (3.4 mL, 24.00 mmol) in dichloromethane (50 mL) was added via cannula a solution of methanesulfonyl chloride (1.55 mL, 20.00 mmol) in dichloromethane (50 mL). The additional was completed in 5 min., the reaction mixture was stirred for another hour at 0°C and then at room temperature for 4 hours. The reaction mixture was washed with water (2 x 30 mL) and the combined aqueous washings backextracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to provide 4.87 g of the crude mesylate.

(iii) To sodium hydride, 80% oil dispersion, previously washed with hexanes (3 x 10 mL), (0.60 g, 25.00 mmol) in anhydrous dimethylformamide (50 mL) was added via cannula a solution of 2-naphthenethanol (3.4 g, 20.00 mmol) in anhydrous dimethylformamide (50 mL). Addition was followed by hydrogen bubbling, the reaction mixture was stirred at room temperature for 90 min. The mesylate as prepared in (ii) above was dissolved in dry dimethylformamide (50 mL) and the resulting solution was added quickly (3 min.) via cannula to the reaction mixture. The reaction mixture was heated up to 90°C in 2 hours, then the temperature was reduced to 40°C and the reaction stirred overnight. The reaction mixture was poured into ice-water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were backwashed with a sodium chloride saturated aqueous solution (300 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* provided 8.1 g of an oil which was dissolved in 1M HCl aqueous solution (50 mL) and the volume completed to 200 mL with water. The acidic aqueous solution was extracted with diethyl ether (2 x 100 mL) and then basified to pH 10 with 50% sodium hydroxide aqueous solution. The basic aqueous solution was extracted with ethyl ether (2 x 100 mL), the combined

organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 3.58 g of the crude free aminoether. The crude product was purified by chromatography column using silica gel 60, 70-230 mesh from BDH Inc. with a mixture of methanol and dichloromethane (2:8, v/v) as eluent to provide the pure free base. The product was dissolved in diethyl ether (50 mL) and converted to the monohydrochloride salt by adding ethereal HCl (50 mL). The solvent was evaporated *in vacuo* to yield 0.75 g of the title compound (not recrystallized).

EXAMPLE 14

(1R,2R)/(1S,2S)-2-(4-MORPHOLINYL)-1-(3,4-DICHLOROPHENETHOXY)
CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #14)

The basic overall approach used to synthesize this compound is analogous to that shown in Figure 1.

(i) (1R,2R)/(1S,2S)-2-(4-Morpholinyl)cyclohexanol: A mixture of cyclohexene oxide (206.5 mL, 2 mol, 98%) and morpholine (175 mL, 2 mol) in water (60 mL) was refluxed for 3.5 h. Morpholine (5.3 mL) was added to the reaction mixture, which was then further refluxed for 1.5 h. in order to complete the reaction. The cooled reaction mixture was then partitioned between 40% NaOH aqueous solution (100 mL) and diethyl ether (200 mL). The aqueous layer was separated from the organic layer and extracted twice more with diethyl ether (2 x 100 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Vacuum distillation yielded 342.3 g (92.4%) of the title compound.

(ii) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)cyclohexanol (40.76 g, 0.22 mol) and triethylamine (36.60 mL, 0.26 mol) in dichloromethane (400 mL) was added dropwise a solution of methanesulfonyl chloride (20.53 mL, 0.26 mol) in dichloromethane (50 mL). The reaction mixture was stirred at 0°C for 45 min. and then at room temperature for 3 hours. The reaction mixture was then washed with water (2 x 100 mL); the combined washings were back-

extracted with dichloromethane (100 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate suitable for the next step without any further purification.

(iii) 3,4-Dichlorophenethyl alcohol: To a solution of lithium
5 aluminum hydride (7.79 g, 195 mmol) in anhydrous diethyl ether (435 mL) was added slowly as a powder, via a solid dropping funnel, 3,4-dichlorophenyl acetic acid (27.20 g, 130 mmol). When the addition was completed, the reaction mixture was refluxed for 12 hours. The reaction was quenched by cautious addition of saturated sodium sulfate aqueous solution (20 mL), the resulting insoluble was then filtered off and the filtrate
10 was concentrated *in vacuo* to yield 25.09 g of the desired alcohol.

(iv) To NaH (6.00 g, 0.2 mol, 80% dispersion in oil) in anhydrous ethylene glycol dimethyl ether (200 mL) was added a solution of 3,4-dichlorophenethyl alcohol (38.87 g, 0.2 mol) in anhydrous ethylene glycol dimethyl ether (100 mL). The resulting mixture was stirred for 3 hours at ambient temperature under argon
15 atmosphere.

(v) The mesylate (ii) in anhydrous ethylene glycol dimethyl ether (100 mL) was added quickly to the alkoxide (iv) and the resulting reaction mixture was readily refluxed for 16 hours. To the cooled reaction mixture was added water (200 mL) and the organic solvent was evaporated *in vacuo*. The resulting aqueous solution
20 was further diluted with water (200 mL) and the pH was adjusted to pH 1.5 with 10% HCl aqueous solution. The acidic aqueous layer was extracted with diethyl ether (500 mL) to eliminate the unreacted 3,4-dichlorophenethyl alcohol. Further basification of the aqueous layer with 5M NaOH aqueous solution to pH 5.7 followed by extraction with diethyl ether provided the crude title compound contaminated with some
25 remaining mesylate (ii). The solvent of the organic extract at pH 5.7 was evaporated *in vacuo*, the residue was then refluxed in a mixture of ethanol-water (1:1, v/v, 200 mL) in the presence of sodium hydride (4.12 g, 0.1 mol) for 2 hours in order to hydrolyzed the remaining mesylate. The cooled reaction mixture was diluted with water (300 mL) and the organic solvent was evaporated *in vacuo*. The pH of the residual aqueous solution
30 was adjusted to pH 5.7 with 6M HCl aqueous solution followed by extraction with

diethyl ether (700 mL). The organic extract was concentrated *in vacuo* to yield the pure aminoether. The residual product was then partitioned between 1M HCl aqueous solution (300 mL) and dichloromethane (300 mL). The acidic aqueous solution was extracted twice more with dichloromethane (2 x 300 mL). The combined organic layers
5 were dried over sodium sulfate, the solvent was evaporated *in vacuo* and the residue was recrystallized from a mixture of ethanol-hexanes (3:7, v/v, 700 mL) to yield 49.3 g of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 15

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(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-(1-NAPHTHENETHOXY)CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #15)

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Synthesis of Compound #15 follows the sequence of reactions shown in Figure 4A and Figure 4B, and is described in detail below.

(i) N-Benzyloxycarbonyl-3-pyrrolidinol: To a chilled (-60°C) solution of (R)-(+)-3-pyrrolidinol (20.0 g, 98%, 224.9 mmol) and triethylamine (79.2 mL, 99%, 562 mmol) in dichloromethane (200 mL) was added dropwise a solution of
20 benzyl chloroformate (33.8 mL, 95%, 224.9 mmol) in dichloromethane (80 mL). After the addition was completed within 45 min, the reaction mixture (a yellow suspension) was allowed to warm up to room temperature and was stirred under argon at room temperature overnight. The reaction mixture was then quenched with 1M HCl aqueous solution (350 mL) and the organic layer was collected. The acidic aqueous layer was
25 extracted with dichloromethane (2 x 150 mL) and the combined organic layers were dried over sodium sulfate. Evaporation *in vacuo* of the solvent provided 59.62 g of pale yellow oil, which was further pumped under high vacuum for 15 min to yield 58.23 g (17% over theoretical yield) of the crude title compound suitable for the next step without any further purification.

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(ii) N-Benzyloxycarbonyl-3-pyrrolidinone: To a chilled (-60°C) solution of oxalyl chloride (23 mL, 98%, 258.6 mmol) in dichloromethane (400 mL)

was added dropwise a solution of anhydrous dimethyl sulfoxide (36.7 mL, 517.3 mmol) in dichloromethane (20 mL) at such a rate to keep the temperature below -40°C. The reaction mixture was then stirred at -60°C for 15 min. Then a solution of N-benzyloxycarbonyl-3-pyrrolidinol (58.22 g, step i, no more than 224.9 mmol) in dichloromethane (80 mL) was added dropwise, keeping the reaction mixture temperature below -50°C. The reaction mixture was then stirred at -60°C for 30 min before adding triethylamine (158.3 mL, 99%, 1.125 mol). The resulting mixture was allowed to warm up to room temperature and then washed with water (600 mL), 1M HCl aqueous solution (580 mL) and water (400 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo* to leave 54.5 g of amber oil, which was further pumped under high vacuum with stirring at room temperature for 25 min. to give 52.08 g (5.6% over theoretical yield) of the crude title compound suitable for the next step without any further purification.

(iii) 7-Benzyloxycarbonyl-1,4-dioxo-7-azaspiro[4.4]nonane:

A mixture of N-benzyloxycarbonyl-3-pyrrolidinone (51.98 g, step ii, no more than 224.9 mmol) and ethylene glycol (18.8 mL, 99+%, 337.4 mmol) in toluene (180 mL) with a catalytic amount of *p*-toluenesulfonic acid monohydrate (1.04 g, 5.4 mmol) was refluxed in a Dean & Stark apparatus for 16 hours. The reaction mixture was then diluted with more toluene (250 mL) and washed with saturated sodium bicarbonate aqueous solution (150 mL) and saturated sodium chloride aqueous solution (2 x 150 mL). The combined aqueous layers were back-extracted with toluene (100 mL). The combined organic layers were dried over sodium sulfate and concentrated *in vacuo* to leave 79.6 g of dark oil. The crude product was dissolved in ethanol (500 mL), and running it through a bed of activated carbon (80 g), decolorized the resulting solution. The charcoal was washed with more ethanol (1000 mL) and toluene (500 mL). The filtrate was concentrated *in vacuo* and further pumped under high vacuum for 1 hour to yield 63.25 g (6.8% over theoretical yield) of the crude title compound suitable for the next step without any further purification.

(iv) 1,4-Dioxo-7-azaspiro[4.4]nonane: A mixture of 7-benzyloxycarbonyl-1,4-dioxo-7-azaspiro[4.4]nonane (34.79 g, step iii, no more than

123.7 mmol) and 10% Pd-C (13.9 g) in ethanol (90 mL) was hydrogenolyzed (60 psi) in a Parr shaker apparatus at room temperature for 1.5 hour. The catalyst was filtered off, the solvent was evaporated *in vacuo* and the residue was pumped under high vacuum for 20 min. to yield 15.86 g of the title compound (yield 99.3%).

5 (v) (1R,2R)/(1S,2S)-2-(1,4-Dioxo-7-azaspiro[4.4]non-7-yl)cyclohexanol: A mixture of 1,4-dioxo-7-azaspiro[4.4]nonane (23.54 g, step iv, no more than 182 mmol), cyclohexene oxide (22.6 mL, 98%, 219 mmol) and water (7.8 mL) was heated at 80°C for 2 hours. The reaction mixture was then partitioned between 40% sodium hydroxide aqueous solution (60 mL) and diethyl ether (120 mL). The
10 basic aqueous layer was extracted twice more with diethyl ether (2 x 120 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo*. The residue was then pumped under high vacuum at 50 °C for 1 hour under stirring (to remove the excess of cyclohexene oxide) to yield 32.79 g of the crude title compound (yield 79.3%).

15 (vi) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)cyclohexanol (27.47 g, 120 mmol, step v) and triethylamine (15.86 g, 156 mmol) in dichloromethane (240 mL) was added dropwise methanesulfonyl chloride (18.23 g, 156 mmol). The reaction mixture was stirred at 0°C for 45 min. and then at room temperature for 3 hours. The reaction mixture was then
20 washed with a mixture of water-saturated sodium bicarbonate aqueous solution (1:1, v/v, 120 mL). The washing layer was collected and was back-extracted with dichloromethane (120 mL). The combined organic extracts were dried over sodium sulfate, the solvent was evaporated *in vacuo* and the residue was pumped under high vacuum for 4 hours to yield the crude mesylate suitable for the next step without any
25 further purification.

(vii) To sodium hydride (4.32 g, 144 mmol) suspended in anhydrous ethylene glycol dimethyl ether (80 mL) was added a solution of 1-naphthenethanol (25.31 g, 144 mmol) in anhydrous ethylene glycol dimethyl ether (80 mL). The resulting mixture was then stirred at room temperature for 4 hours.

(viii) (1R,2R)/(1S,2S)-2-[1,4-dioxo-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane: A solution of mesylate (vi) in anhydrous ethylene glycol dimethyl ether (80 mL) was added quickly to the alkoxide (vii) and the resulting mixture was readily heated to reflux under argon for 66 hours. The cooled reaction mixture was quenched with water (200 mL) and the organic solvent was evaporated *in vacuo*. The remaining aqueous solution was diluted with water (500 mL) and acidified with 10% HCl aqueous solution to pH 0.5. The acidic aqueous layer was extracted with diethyl ether (2 x 500 mL) in order to extract unreacted 1-naphthenethanol. The pH of the aqueous solution was adjusted to pH 4.8 with 5M NaOH aqueous solution and then extracted with diethyl ether (600 mL). The aqueous solution was further basified to pH 5.7 and extracted with diethyl ether (600 mL). The same procedure was repeated at pH 6.5 and 12.1. Analysis by gas chromatography of the different ether extracts showed that organic extracts at pH 4.8, 5.7 and 6.5 contained the title compound whereas ether extract at pH 12.1 contained only unknown impurities. The organic extracts at pH 4.8, 5.7 and 6.5 were combined and dried over sodium sulfate. The solvent was evaporated *in vacuo* and the residue was pumped under high vacuum for 3.5 hours to yield 35.82 g (75% yield) of the title compound suitable for the next step without any further purification.

(ix) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane monohydrochloride: A solution of (1R,2R)/(1S,2S)-2-[1,4-dioxo-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane (13.73 g, 36.0 mmol, step vi) with 6M HCl aqueous solution (50 mL) in 2-butanone (200 mL) was refluxed for 12 hours. The butanone was evaporated *in vacuo* and the residual aqueous solution was diluted to 250 mL with water. The aqueous solution was extracted with diethyl ether (2 x 200 mL) and then with dichloromethane (2 x 200 mL). The pooled dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residual oil was azeotropically dried with toluene. The resulting sticky product was vigorously stirred overnight in diethyl ether (500 mL) with occasional scratching to trigger crystallization of the reaction product. The resulting solid was collected and solubilized in a small amount of dichloromethane (~10 mL),

addition of a large quantity of diethyl ether (~400 mL) triggered recrystallization. The solid was collected, dried under high vacuum for 3 hours to yield 9.3 g (76% yield) of the title compound, having the elemental analysis indicated in Table 1.

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EXAMPLE 16

(1R,2R)/(1S,2S)-2-(1-ACETYLPIPERAZINYL)-1-(2-NAPHTHENETHOXY)CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #16)

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Compound #16 was prepared according to a procedure similar as the one depicted in Figure 1 and further detailed in Example 14.

(i) (1R,2R)/(1S,2S)-2-(1-Acetylpiperazinyl)-1-cyclohexanol: A mixture of 1-acetylpiperazine (5 g, 39 mmol) and cyclohexene oxide (3.95 mL, 39 mmol) in water (1.2 mL) was refluxed for 16 hours. The cooled reaction mixture was partitioned between 40% NaOH aqueous solution (20 mL) and diethyl ether (2 x 20 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 7.63 g of the title compound as white crystals (87% yield)

(ii) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(1-acetylpiperazinyl)-1-cyclohexanol (3.65 g, 16.2 mmol) and triethylamine (3.4 mL, 24 mmol) in dichloromethane (50 mL) was added dropwise a solution of methanesulfonyl chloride (1.55 mL, 20 mmol) in dichloromethane (50 mL). The reaction mixture was stirred at 0°C for one hour and then allowed to warm up to ambient temperature. The reaction mixture was then washed with water (2 x 50 mL) and the combined washings were back-extracted with dichloromethane (50 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate suitable for the next step without any further purification.

(iii) To a suspension of sodium hydride (0.8 g, 24 mmol, previously washed with hexanes (2 x 15 mL)) in anhydrous dimethylformamide (50 mL) was added a solution of 2-naphthenethanol in anhydrous dimethylformamide (50 mL). The resulting mixture was stirred at room temperature for 30 min.

(iv) (1R,2R)/(1S,2S)-2-(1-Acetylpiperazinyl)-1-(2-naphthenethoxy)cyclohexane monohydrochloride: the mesylate (ii) in solution in anhydrous dimethylformamide (50 mL) was added quickly to the alkoxide mixture (iii) and the resulting mixture was heated to 80°C for 16 hours. The cooled reaction mixture was poured into ice water (800 mL) and extracted with ethyl acetate (3 x 200 mL). The combined organic extracts were back-washed with brine (200 mL) and the solvent was evaporated *in vacuo*. The residual oil was taken up with water (80 mL) and the resulting aqueous solution was acidified to pH 2 with 6M HCl aqueous solution. The acidic aqueous solution was extracted with diethyl ether (3 x 40 mL) in order to extract the unreacted 2-naphthenethanol. The pH of the aqueous layer was adjusted to pH10 with 50% NaOH aqueous solution and extracted with diethyl ether (3 x 40 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude free aminoether. Purification by column chromatography of silica gel using a mixture of ethyl acetate-dichloromethane (1:1, v/v) as eluent provided the pure free base. Conversion to the hydrochloride salt was accomplished with ethereal HCl followed by recrystallization in a mixture of ethanol-diethyl ether provided the title compound, having the elemental analysis indicated in Table 1.

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EXAMPLE 17

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-(2,6-DICHLOROPHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #17)

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Compound #17 was prepared in 10 steps according to the procedure described in Example 16. Steps (i) to (v) was identical to those in Example 16.

(vi) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(1,4-dioxa-7-azaspiro[4.4]non-7-yl)cyclohexanol (27.77 g, 120 mmol) and triethylamine (22 mL, 156 mmol) in dichloromethane (240 mL) was added methanesulfonyl chloride (12.32 mL, 156 mmol). The reaction mixture was stirred at 0°C for 45 min. and then at room

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temperature for 3 hours. The reaction mixture was washed with water (2 x 100 mL) and the combined washings were back-extracted with dichloromethane (120 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate which was further pumped under high vacuum for 4 hours prior to use in step ix.

(vii) 2,6-Dichlorophenethyl alcohol: a suspension of lithium aluminum hydride (13.75 g, 365.75 mmol) in anhydrous diethyl ether (500 mL) was added via a powder addition funnel 2,6-dichlorophenylacetic acid (50 g, 243.75 mmol). The resulting reaction mixture was refluxed for 16 hours and then quenched by slow addition of a sodium sulfate saturated aqueous solution (25 mL). The resulting slurry was stirred for 3 hours and then filtered, the insoluble was carefully washed with diethyl ether (2 x 100 mL). The combined ether filtrates were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 38.6 g (85% yield) of the title compound.

(viii) To sodium hydride (144 mmol, 4.32 g, 80% oil dispersion) in anhydrous ethylene glycol dimethyl ether (80 mL) was added a solution of 2,6-dichlorophenethyl alcohol (27.65 g, 144 mmol) in anhydrous ethylene glycol dimethyl ether (80 mL). The resulting mixture was stirred at room temperature under argon atmosphere for 4 hours.

(ix) (1R,2R)/(1S,2S)-2-[1,4-Dioxo-7-azaspiro[4.4]non-7-yl]-1-(2,6-dichlorophenethoxy)cyclohexane: The mesylate (vi) in anhydrous ethylene glycol dimethyl ether (80 mL) was added quickly to the alkoxide mixture (viii) and the resulting mixture was readily refluxed for 66 hours. The cooled reaction mixture was poured into water (200 mL) and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was diluted with more water to a volume of 700 mL, acidified to pH 0.5 with 6M HCl aqueous solution and extracted with diethyl ether (2 x 600 mL). The pH of the aqueous layer was adjusted to pH 5.9 and then the aqueous solution was extracted with diethyl ether (700 mL). The organic extract was dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 34.0 g of the title compound (70% yield).

(x) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(2,6-dichlorophenoxy)cyclohexane monohydrochloride: A mixture of (1R,2R)/(1S,2S)-2-[1,4-dioxo-7-azaspiro[4.4]non-7-yl]-1-(2,6-dichlorophenoxy)cyclohexane (15.85 g, 38.9 mmol, step ix) and 6M HCl aqueous solution (100 mL) in 2-butanone (400 mL) was refluxed for 16 hours. The cooled reaction mixture was diluted with water (100 mL) and the organic solvent was evaporated *in vacuo*. The organic layer was further diluted with water (400 mL), extracted with diethyl ether (500 mL) and with dichloromethane (2 x 600 mL). The combined dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Azeotropic distillation with toluene provided the title compound which was further dried under high vacuum for 15 min. The hydrochloride salt was crystallized by triturating in diethyl ether, the crystals were collected and recrystallized from a mixture of ethanol-diethyl ether to yield 11.85 g of pure product (77% yield), having the elemental analysis indicated in Table 1.

EXAMPLE 18

(1R,2R)/(1S,2S)-2-[1,4-DIOXA-7-AZASPIRO[4.4]NON-7-YL]-1-(1-NAPHTHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #18)

(1R,2R)/(1S,2S)-2-[1,4-Dioxo-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane (1.2 g, 3.14 mmol, from Example 15, step (viii)) in diethyl ether (80 mL) was treated with ethereal HCl. The solvent was evaporated *in vacuo* and the residue was taken up with diethyl ether, triturating gave a solid, which was collected and precipitated from a mixture of dichloromethane-diethyl ether to yield 0.85 g of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 19

(1R,2S)/(1S,2R)-2-(4-MORPHOLINYL)-1-[(2-
TRIFLUOROMETHYL)PHENETHOXY]CYCLOHEXANE MONOHYDROCHLORIDE
5 (COMPOUND #19)

(i) 2-(4-Morpholinyl)cyclohexanone: To a chilled (-70°C) solution of oxalyl chloride (20 mL, 0.23 mol) in dichloromethane (500 mL) was added dropwise a solution of anhydrous dimethylsulfoxide (34 mL, 0.48 mol) in dichloromethane (50 mL) and the resulting mixture was stirred for 5 min. at a temperature below -60°C. Then a solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)cyclohexanol (37.05 g, 0.2 mol) in dichloromethane (50 mL) was added dropwise in order to maintain the reaction temperature below -60°C and the reaction mixture was stirred for 15 min. Triethylamine (140 mL) was added dropwise to the reaction mixture, keeping the
15 reaction temperature below -50°C, and then the reaction mixture was allowed to warm up to room temperature. The reaction mixture was poured into water (600 mL) and the aqueous layer was separated and extracted with dichloromethane (2 x 500 mL). The combined organic layers were dried over sodium sulfate and the solvent was removed *in vacuo*. Vacuum distillation yielded 35.1 g (96% yield) of the title compound.

(ii) 2-(4-Morpholinyl)cyclohexanol: To a chilled (0°C) suspension of sodium borohydride (2.14 g, 56 mmol) in isopropanol (120 mL) was added a solution of 2-(4-morpholinyl)cyclohexanol (24.7 g, 135 mmol, step i) in isopropanol (80 mL). The resulting reaction mixture was stirred at 0°C for 10 min. and then 30 min. at ambient temperature. Water (200 mL) was added to the reaction mixture and the organic solvent
25 was evaporated *in vacuo*. The residual aqueous solution was then extracted with ethyl acetate (4 x 50 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield 22.48 g of the title compound suitable for the next step without any further purification.

(iii) (1S,2R)/(1R,2S)-2-(4-Morpholinyl)cyclohexyl
30 2-(trifluoromethyl)phenylacetate: A mixture of 2-(4-morpholinyl)cyclohexanol (7.41 g, 40 mmol, step ii), 2-(trifluoromethyl)phenylacetic acid (10.21 g, 49 mmol) and p-

toluenesulfonic acid monohydrate (40 mg) in toluene (60 mL) was refluxed in a Dean & Stark apparatus for 48 hours. To the cooled reaction mixture was added saturated sodium bicarbonate aqueous solution (40 mL), the aqueous layer was separated and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield a mixture of (1S,2R)/(1R,2S)-2-(4-morpholinyl)cyclohexyl 2-(trifluoromethyl)phenylacetate and (1R,2R)/(1S,2S)-2-(4-morpholinyl)cyclohexyl 2-(trifluoromethyl)phenylacetate. Chromatography by dry column of the *cis/trans* mixture with mixtures of ethyl acetate-hexanes (+ 0.5% isopropylamine v/v) as eluents provided 3.19 g of the crude title compound contaminated by the starting material 2-(4-morpholinyl)cyclohexanol. The crude product was partitioned between dichloromethane (30 mL) and 0.5M HCl aqueous solution (7 mL). The aqueous layer was separated and further extracted with dichloromethane (2 x 18 mL). The combined organic layers were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Recrystallization from a mixture of ethanol-hexanes yielded 2.78 g of the title compound.

(iv) (1S,2R)/(1R,2S)-2-(4-Morpholinyl)-1-[(2-trifluoromethyl)phenethoxy]cyclohexane monohydrochloride: To a mixture of (1S,2R)/(1R,2S)-2-(4-morpholinyl)cyclohexyl 2-(trifluoromethyl)phenylacetate (1.64 g, 4.28 mmol, step iii) and sodium borohydride (332 mg, 8.70 mmol) in anhydrous tetrahydrofuran (35 mL) under reflux was added a solution of boron trifluoride diethyl etherate (8.2 mL, 65 mmol) over 1.5 hour. The reaction mixture was quenched by addition of water (~70 mL), the organic solvent was evaporated *in vacuo* and the pH of the residual aqueous solution was adjusted to pH 9.6. The aqueous layer was extracted with diethyl ether (2 x 70 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. The residue was then partitioned between 0.5M HCl aqueous solution (50 mL) and diethyl ether (2 x 50 mL). The aqueous solution was basified to pH 5.9 and extracted with diethyl ether (50 mL). The organic layer was collected, dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude free aminoether. The free base was converted to the hydrochloride salt by partition between 0.5M HCl aqueous solution (10 mL) and

dichloromethane (10 mL). The acidic aqueous solution was extracted once more with dichloromethane (10 mL), the combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*. Recrystallization from a mixture of ethanol-hexanes yielded 636 mg (38% yield) of the title compound, having the
5 elemental analysis indicated in Table 1.

EXAMPLE 20

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-[3-
10 (CYCLOHEXYL)PROPOXY]CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #20)

(i) 3-Cyclohexyl-1-propyl bromide: To the chilled (0°C) 3-cyclohexyl-1-propanol (5 g, 35.15 mmol) was added slowly a solution of phosphorus tribromide (1.1 mL, 17.6 mmol) in dichloromethane (2 mL). Upon completion of the
15 addition, the reaction mixture was allowed to warm up to room temperature and was stirred for 4 hours. The reaction was quenched by addition of saturated sodium bicarbonate aqueous solution (5 mL) and 10% NaOH (10 mL). The resulting mixture was extracted with diethyl ether (3 x 50 mL), the combined organic extracts were dried
20 over sodium sulfate and the solvent was evaporated *in vacuo* to provide an oil. Vacuum distillation yielded 3.4 g (47% yield) of the title compound.

(ii) (1R,2R)/(1S,2S)-2-[1,4-Dioxo-7-azaspiro[4.4]non-7-yl]-1-[3-(cyclohexyl)propoxy]cyclohexane: To a suspension of sodium hydride (200 mg, 8.33 mmol) in anhydrous dimethylformamide (20 mL) was added a solution of
25 (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)cyclohexanol (1.5 g, 6.6 mmol) in anhydrous dimethylformamide (10 mL). The resulting mixture was stirred at room temperature for 30 min. and then a solution of 3-(cyclohexyl)propyl bromide (1.67 g, 8.15 mmols) in anhydrous dimethylformamide was quickly added. The reaction mixture was stirred at room temperature for 16 hours. The reaction mixture was poured
30 into water (200 mL) and then extracted with ethyl acetate (3 x 50 mL). The combined organic extracts were back-washed with brine (50 mL) and the solvent was evaporated

in vacuo. The residue was taken up with water (50 mL) and the pH was adjusted to pH 1.0 with 6M HCl aqueous solution. The acidic aqueous solution was extracted with diethyl ether (2 x 50 mL), then basified to pH 5.0-5.5 with 5M NaOH aqueous solution and extracted with diethyl ether (3 x 50 mL). The combined organic extracts at pH 5.0-5.5 were concentrated *in vacuo* to provide the crude title compound suitable for the next step without any further purification.

(iii) (1R,2S)/(1S,2R)-2-(3-Ketopyrrolidinyl)-1-[3-(cyclohexyl)propoxy]cyclohexane monohydrochloride: (1R,2R)/(1S,2S)-2-[1,4-Dioxo-7-azaspiro[4.4]non-7-yl]-1-[3-(cyclohexyl)propoxy]cyclohexane (ii) in a mixture of 6M HCl aqueous solution-butanone (1:4, v/v, 100 mL) was refluxed for 16 hours. The cooled reaction mixture was concentrated *in vacuo* and the residual aqueous solution was diluted with water (~50 mL). The acidic aqueous solution was extracted with diethyl ether (50 mL) and then with dichloromethane (3 x 50 mL). The dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to provide the crude title compound. The hydrochloride salt was crystallized by triturating in a mixture of diethyl ether-hexanes (1:1, v/v, ~200 mL) and then precipitated from a mixture of dichloromethane-diethyl ether-hexanes to yield 0.8 g of the title compound, having the elemental analysis indicated in Table 1.

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EXAMPLE 21

(1R,2R)/(1S,2S)-2-(3-ACETOXPYRROLIDINYL)-1-(1-NAPHTHENETHOXY)CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #21)

25

(i) (1R,2R)/(1S,2S)-2-(3-Hydroxypyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane monohydrochloride: To a chilled (0°C) solution of sodium borohydride in isopropanol (20 mL) was added a solution of (1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane monohydrochloride (1.4 g, 3.75 mmol) in isopropanol (30 mL). The resulting mixture was stirred at 0°C for 15 min. and then 30 min. at room temperature. The reaction was quenched by addition of water,

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the reaction mixture was evaporated to dryness and the residue was washed with dichloromethane (2 x 20 mL). The dichloromethane washings were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the title compound.

(ii) (1R,2R)/(1S,2S)-2-(3-Acetoxypyrrolidinyl)-1-(1-

5 naphthenethoxy)cyclohexane monohydrochloride: The intermediate alcohol (i) was then refluxed in acetic anhydride (15 mL) for 2 hours. The excess acetic anhydride was removed *in vacuo*; the residue was taken up with water (100 mL) and extracted with diethyl ether (2 x 30 mL). The aqueous solution was basified to pH 8.0 and extracted with diethyl ether (3 x 50 mL). The combined organic extracts were dried over sodium
10 sulfate and concentrated *in vacuo*. The residual oil was dissolved in a small amount of dichloromethane and a large volume of diethyl ether was added in order to trigger crystallization of 1.0 g (65% yield) of the title compound, having the elemental analysis indicated in Table 1.

15

EXAMPLE 22

(1R,2R)/(1S,2S)-2-(4-MORPHOLINYL)-1-[(2,6-
DICHLOROPHENYL)METHOXY]CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #22)

20

Compound #22 was prepared according to the Williamson ether synthesis. To a suspension of sodium hydride, 80% oil dispersion (337 mg, 11 mmol) in ethylene glycol dimethyl ether (20 mL) was added a solution of (1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-cyclohexanol (2.0 g, 10.8 mmol) in ethylene glycol dimethyl ether
25 (10 mL). The resulting reaction mixture was stirred at room temperature under argon atmosphere for 3 hours, then a solution of 2,6-dichlorobenzyl bromide in ethylene glycol dimethyl ether (10 mL) was added and the reaction mixture was refluxed for 16 hours. The cooled reaction mixture was poured into water (40 mL) and the organic solvent was evaporated *in vacuo*. The residual aqueous solution was diluted with more
30 water (60 mL) and acidified to pH 0.5 with 6M HCl aqueous solution. The acidic aqueous solution was extracted with diethyl ether (2 x 40 mL) and then the pH was

adjusted to pH 5.5. Extraction with diethyl ether (3 x 50 mL) followed by drying over sodium sulfate and concentration *in vacuo* provided the pure aminoether. The hydrochloride salt was precipitated by treatment of the free base with ethereal HCl. Recrystallization from a mixture of acetone-methanol-diethyl ether yielded 2.6 g (68%
5 yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 23

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-[(2,6-
10 DICHLOROPHENYL)METHOXY]CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #23)

Compound #23 was prepared in 7 steps according to the procedure detailed in Example 15. Steps (i) to (v) was identical to the ones described in Example
15 15. The ether synthesis (step vi) was carried out according to the Williamson ether synthesis as in Example #22.

(vi) (1R,2R)/(1S,2S)-2-[1,4-Dioxo-7-azaspiro[4.4]non-7-yl]-1-[(2,6-dichlorophenyl)methoxy] cyclohexane: To a suspension of sodium hydride, 80% oil dispersion (222 mg, 7.25 mmol) in ethyleneglycol dimethyl ether (20 mL) was added a
20 solution of (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)cyclohexanol (1.5 g, 6.60 mmol, step (v) of Example 15) in ethylene glycol dimethyl ether (10 mL). The resulting mixture was stirred at room temperature for 2 hours and then a solution of 2,6-dichlorobenzyl bromide (1.9 g, 7.9 mmol) in ethylene glycol dimethyl ether (10 mL) was added. The reaction mixture was refluxed for 16 hours under argon atmosphere,
25 the solvent was evaporated *in vacuo* and the residue was taken up with water (70 mL). The aqueous solution was acidified to pH 0.5 with 6M HCl aqueous solution and then extracted with diethyl ether (2 x 40 mL). Basification of the aqueous solution to pH 4.5-5.5, followed by extraction with diethyl ether (4 x 40 mL), drying of the combined organic extracts over sodium sulfate and evaporation of the solvent *in vacuo* provided
30 the intermediate title compound.

(vii) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane monohydrochloride: The ketal intermediate (step vi) in a mixture of 6M HCl-butanone (1:4, v/v, 100 mL) was refluxed for 16 hours. The butanone was evaporated *in vacuo* and the residual aqueous layer was diluted with more
5 water (100 mL). The acidic aqueous layer was extracted with diethyl ether (2 x 40 mL) and then with dichloromethane (3 x 40 mL). The combined dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to provide the crude title compound. The product was crystallized by triturating in diethyl ether and reprecipitated from a mixture of dichloromethane-diethyl ether to yield 1.8 g (72%
10 yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 24

(1R,2R)/(1S,2S)-2-(3-HYDROXYPYRROLIDINYL)-1-(2,6-
15 DICHLOROPHENETHOXY)CYCLOHEXANE MONOHYDROCHLORIDE
(COMPOUND #24)

To a solution of compound #17 (5.0 g, 12.7 mmol) in isopropanol (120 mL) was added sodium borohydride (2.0 g, 52.8 mmol) as a powder and the resulting
20 mixture was stirred at room temperature until completion of the reaction. The reaction was quenched with water (40 mL) and then concentrated to dryness. The residue was washed with dichloromethane (50 mL); the filtrate was dried over sodium sulfate, concentrated *in vacuo* to provide the title compound, which crystallized after 3 hours under high vacuum. Elemental analysis results of the product is shown in Table 1.

EXAMPLE 25

(1R,2R)/(1S,2S)-2-(3-KETOPYRROLIDINYL)-1-(2,2-DIPHENYLETHOXY)CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #25)

Compound #25 was prepared in 10 steps according to a procedure identical to the one described in Examples 15 and 17. Steps (i) to (v) were identical to Example 15.

(vi) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)cyclohexanol (2.0 g, 8.8 mmol) and triethylamine (2.1 mL, 15 mmol) in dichloromethane (30 mL) was added methanesulfonyl chloride (0.9 mL, 11.44 mmol). The reaction mixture was stirred at 0°C for 45 min. and then at room temperature for 3 hours. The reaction mixture was diluted with dichloromethane (25 mL), washed with water (2 x 25 mL) and the combined washings were back-extracted with dichloromethane (25 mL). The combined organic extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo* to yield the crude mesylate which was further pumped under high vacuum for 30 min. prior to use in step ix.

(vii) (2,2-Diphenyl)ethyl alcohol: To lithium aluminum hydride (2.85 g, 23.56 mmol) in anhydrous diethyl ether (150 mL) was added, as a powder, diphenylacetic acid (5.0 g, 56 mmol). The resulting reaction mixture was gently refluxed for one hour. The reaction was quenched with sodium sulfate saturated aqueous solution and the resulting precipitate was filtered off. The filtrate was concentrated *in vacuo* to yield 4.0 g (86% yield) of the title compound.

(viii) To sodium hydride, previously washed with hexanes, (253 mg, 10.56 mmol) in suspension in ethylene glycol dimethyl ether (15 mL) was added a solution of 2,2-diphenylethyl alcohol (2.09 g, 10.56 mmol, step vii) in ethylene glycol dimethyl ether (15 mL). The resulting mixture was stirred at room temperature under argon atmosphere for 30 min.

(ix) (1R,2R)/(1S,2S)-2-(1,4-Dioxo-7-azaspiro[4.4]non-7-yl)-1-(2,2-diphenylethoxy)cyclohexane: The mesylate (vi) in ethylene glycol dimethyl ether (20 mL) was added quickly to the alkoxide (viii) and the reaction mixture was refluxed for

5 days. The cooled reaction mixture was concentrated *in vacuo*, the residue was taken up with water (50 mL) and the pH was adjusted to pH 1.0 with 6M HCl aqueous solution. The acidic aqueous solution was extracted with diethyl ether (2 x 50 mL), the aqueous layer was collected and basified to pH 6.0. Extraction with diethyl ether (2 x 50 mL) followed by drying over sodium sulfate and evaporation of the solvent *in vacuo* yielded 1.55 g (43% yield) of the title compound.

(x) (1R,2R)/(1S,2S)-2-(3-Ketopyrrolidinyl)-1-(2,2-diphenylethoxy)cyclohexane monohydrochloride: A mixture of (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)-1-(2,2-diphenylethoxy)cyclohexane (1.55 g, 3.8 mmol) in 6M HCl-butanone (1:4, v/v, 50 mL) was refluxed for 2 hours. The butanone was evaporated *in vacuo* and the residue was taken up with water (50 mL). The aqueous solution was extracted with diethyl ether (2 x 50 mL); the aqueous layer was collected and extracted with dichloromethane (2 x 50 mL). The combined dichloromethane extracts were dried over sodium sulfate and concentrated *in vacuo* to yield the crude title compound. The product was crystallized by triturating in diethyl ether and reprecipitated from a mixture of dichloromethane-diethyl ether to yield 1.21 g (80% yield) of the title compound, having the elemental analysis indicated in Table 1.

EXAMPLE 26

(1R,2R)/(1S,2S)-2-(3-THIAZOLIDINYL)-1-(2,6-DICHLOROPHENETHOXY)CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #26)

(i) (1R,2R)/(1S,2S)-2-(3-Thiazolidinyl)cyclohexanol: To anhydrous magnesium perchlorate (12.93 g, 53.3 mmol) was added a solution of cyclohexene oxide (6.1 mL, 58.6 mmol) in anhydrous acetonitrile (25 mL) and the resulting mixture was stirred at room temperature for 20 min. Then a solution of thiazolidine (5.16 g, 55.0 mmol) in anhydrous acetonitrile was added and the reaction mixture was heated at 35°C for 16 hours. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between water (350 mL) and diethyl ether (350 mL). The aqueous layer was

separated and extracted once more with diethyl ether (350 mL). The combined organic extracts were dried over sodium sulfate and concentrated *in vacuo* to provide the crude product. The crude aminoalcohol was purified by dry-column chromatography with a mixture of ethyl acetate-hexanes (1:1, v/v) as eluent to yield 4.83 g (47% yield) of the
5 title compound.

(ii) To a chilled (0°C) solution of (1R,2R)/(1S,2S)-2-(3-thiazolidinyl)cyclohexanol (3.17 g, 16.9 mmol) and triethylamine (3.08 mL, 22.0 mmol) in dichloromethane (30 mL) was added dropwise methanesulfonyl chloride (1.74 mL, 22.0 mmol). The reaction mixture was stirred at 0°C for one hour and then at
10 ambient temperature for 3 hours. The reaction mixture was diluted with dichloromethane (20 mL) and washed with water (2 x 30 mL). The combined washings were back-extracted with dichloromethane (25 mL) and the combined organic extracts were dried over sodium sulfate. Evaporation of the solvent *in vacuo* yielded the mesylate suitable for the next step without any further purification.

(iii) To sodium hydride, 80% oil dispersion (608 mg, 20.28 mmol) in ethylene glycol dimethyl ether (30 mL) was added a solution of 2,6-dichlorophenethyl alcohol (3.87 g, 20.28 mmol, example 4, step vii) in ethyleneglycol dimethyl ether (15 mL). The resulting mixture was stirred at room temperature under argon atmosphere
15 for 2 hours.

(iv) (1R,2R)/(1S,2S)-2-(3-Thiazolidinyl)-1-(2,6-
dichlorophenethoxy)cyclohexane monohydrochloride: The mesylate (ii) in ethylene glycol dimethyl ether (15 mL) was added quickly to the alkoxide (iii) and the reaction mixture was refluxed for 40 hours. The cooled reaction mixture was poured into water (100 mL) and the organic solvent was evaporated *in vacuo*. The residual aqueous
20 solution was diluted with more water (100 mL) and the pH was adjusted to pH 1.5. The acidic aqueous solution was extracted with diethyl ether (3 x 100 mL), the combined organic extracts were dried over sodium sulfate and the solvent was removed *in vacuo* to provide the crude free base. The product was purified by dry-column chromatography with a mixture of ethyl acetate-hexanes (1:10, v/v) as eluent to yield
25 2.4 g of the crude free aminoether. The pure product (1.0 g) was converted to the
30

hydrochloride salt by treatment with ethereal HCl and the resulting salt was recrystallized from a mixture of acetone-diethyl ether to yield 0.69 g of the title compound, having the elemental analysis indicated in Table 1.

5

EXAMPLE 27

(1R,2S)/(1S,2R)-2-(3-KETOPYRROLIDINYL)-1-(1-NAPHTHENETHOXY)CYCLOHEXANE
MONOHYDROCHLORIDE
(COMPOUND #27)

10

Compound #27 was prepared in 8 steps according to the synthetic scheme depicted in Figure 3. Steps (i) to (iv) was identical to those described in Example 15.

(v) (1R,2R)/(1S,2S)-1-(1-Naphthenethoxy)-2-cyclohexanol: To
15 anhydrous magnesium perchlorate (270 mg, 1.2 mmol) in anhydrous acetonitrile (1.7 mL) was added cyclohexene oxide (0.12 g, 1.2 mmol). The resulting mixture was stirred for 15 min. at room temperature and then 1-naphthenethanol (2.7 g, 10.15 mmol) was added. The reaction mixture was refluxed and more cyclohexene oxide (2.0 mL, 2.0 g, 20 mmol) was added to the refluxing reaction mixture at a rate of 0.4 mL/hour.
20 Reflux was stopped after 16 hours and the cooled reaction mixture was partitioned between diethyl ether (50 mL) and saturated sodium bicarbonate aqueous solution (30 mL). The aqueous layer was separated and extracted twice more with diethyl ether (2 x 40 mL). The combined organic extracts were back-washed with water (15 mL), brine (15 mL) and dried over sodium sulfate. Evaporation of the solvent *in vacuo* yielded the
25 crude title compound suitable for the next step without any further purification.

(vi) 1-(1-Naphthenethoxy)-2-cyclohexanone: To a solution of
(1R,2R)/(1S,2S)-2-(1-naphthenethoxy)-1-cyclohexanol (1.0 g, step v) in
dimethylformamide (20 mL) was added pyridinium dichromate (5.0 g, 13.2 mmol) in
small portions and the resulting reaction mixture was stirred at room temperature for 16
30 hours. The reaction mixture was poured into water (100 mL) and the resulting slurry was extracted with diethyl ether (3 x 50 mL). The combined organic extracts were

back-washed with 1M NaOH aqueous solution (30 mL), brine (30 mL) and dried over sodium sulfate. Evaporation of the solvent provided 1.0 g of the crude title compound suitable for the next step of the reaction.

- (vii) (1R,2S)/(1S,2R)-2-(1,4-Dioxo-7-azaspiro[4.4]non-7-yl)-1-(1-naphthenethoxy)cyclohexane: To a solution of 1,4-dioxo-7-azaspiro[4.4]nonane (5.17 g, 40 mmol) and 1-(1-naphthenethoxy)-2-cyclohexanone (1.79 g, 6.58 mmol, step vi, 77% pure) in anhydrous methanol (10 mL) was added 5N HCl methanolic solution (2.7 mL) and then sodium cyanoborohydride (397 mg, 6 mmol). The reaction mixture was further diluted with anhydrous methanol (7 mL) and stirred at room temperature for 16 hours. The reaction mixture was quenched by addition of 6M HCl aqueous solution (40 mL), the organic solvent was evaporated *in vacuo*, the residual aqueous solution was diluted to 100 mL with water and the pH was adjusted to pH 0.5 with 6M HCl aqueous solution. The acid aqueous layer was extracted with diethyl ether (100 mL); the aqueous layer was separated and basified to pH 6.7 with 5M NaOH aqueous solution. Extraction with diethyl ether (100 mL), followed by drying over sodium sulfate and evaporation of the solvent *in vacuo* provided, after purification by dry-column chromatography with mixtures of ethyl acetate-hexanes (1:9 to 1:6, v/v, +0.5% v/v isopropylamine) as eluents, 1.28 g of crude (1R,2S)/(1S,2R)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)-1-(1-naphthenethoxy)cyclohexane and (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)-1-(1-naphthenethoxy)cyclohexane. Separation of (1R,2S)/(1S,2R)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)-1-(1-naphthenethoxy)cyclohexane from (1R,2R)/(1S,2S)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)-1-(1-naphthenethoxy)cyclohexane was performed by preparative HPLC (Waters Delta Prep 4000, PrePak cartridge 40 x 100 mm, isopropanol-hexanes (2:98, v/v, + 0.05% v/v diethylamine)) to yield 590 mg of the title compound.

- (viii) (1R,2S)/(1S,2R)-2-(3-Ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane monohydrochloride: A mixture of (1R,2S)/(1S,2R)-2-(1,4-dioxo-7-azaspiro[4.4]non-7-yl)-1-(1-naphthenethoxy)cyclohexane (480 mg, 1.23 mmol, step vii) in 6M HCl aqueous solution-butanone (1:4, v/v, 40 mL) was refluxed for 2 hours. The organic solvent was evaporated *in vacuo*, the residual aqueous solution

was diluted to 50 mL with water and extracted twice with diethyl ether (2 x 50 mL) and then thrice with dichloromethane (3 x 50 mL). The combined dichloromethane extracts were dried over sodium sulfate and the solvent was evaporated *in vacuo*, the residual oil was further dried by azeotropic distillation of toluene. The title compound was
5 crystallized by triturating in hexanes (430 mg, 93% yield), *and has* elemental analysis indicated in Table 1.

Table 1

Compound	Formula	Calculated	Found
#1	$C_{22}H_{30}NO_2Cl$	C 70.29, H 8.04, N 3.73%	C 69.36, H 8.17, N 3.73%
#2	$C_{22}H_{30}NO_2Cl$	C 70.29, H 8.04, N 3.73%	C 69.78, H 8.06, N 3.56%
#3	$C_{18}H_{27}NO_2BrCl$	C 53.41, H 6.72, N 3.46%	C 53.16, H 6.77, N 3.35%
#4	$C_{22}H_{30}NO_3Cl$	C 67.42, H 7.72, N 3.57%	C 67.31, H 7.75, N 3.59%
#5	$C_{18}H_{27}NO_3BrCl$	C 51.38, H 6.47, N 3.33%	C 51.38, H 6.21, N 3.28%
#6	$C_{20}H_{32}NO_4Cl$	C 62.24, H 8.36, N 3.63%	C 61.69, H 8.64, N 3.63%
#7	$C_{22}H_{30}NOCl$	C 73.41, H 8.40, N 3.89%	C 73.26, H 8.64, N 3.94%
#8	$C_{20}H_{28}NO_2SCl$	C 62.89, H 7.39, N 3.67%	C 61.94, H 7.42, N 3.70%
#9	$C_{20}H_{28}NO_2SCl$	C 62.89, H 7.39, N 3.67%	C 62.53, H 7.56, N 3.64%
#10	$C_{18}H_{27}NO_2BrCl$	C 53.41, H 6.72, N 3.46%	C 53.29, H 6.94, N 3.57%
#11	$C_{18}H_{27}NO_2BrCl$	C 53.41, H 6.72, N 3.46%	C 52.61, H 7.46, N 4.01%
#12	$C_{21}H_{34}NO_4Cl$	C 63.06, H 8.57, N 3.50%	C 62.45, H 8.41, N 3.45%
#14	$C_{18}H_{26}NO_2Cl_3$	C 54.77, H 6.64, N 3.55%	C 58.80, H 6.85, N 3.51%
#15	$C_{22}H_{28}NO_2Cl$	C 70.67, H 7.55, N 3.75%	C 70.12, H 7.55, N 3.73%
#16	$C_{24}H_{33}N_2O_2Cl \cdot H_2O$	C 63.63, H 8.23, N 6.18%	C 62.93, H 8.56, N 6.05%
#17	$C_{18}H_{24}NO_2Cl_3$	C 55.05, H 6.16, N 3.57%	C 54.39, H 6.30, N 3.49%
#18	$C_{24}H_{32}NO_3Cl$	C 68.97, H 7.72, N 3.35%	C 68.49, H 7.64, N 3.31%
#19	$C_{19}H_{27}NO_2ClF_3$	C 57.94, H 6.91, N 3.56%	C 57.75, H 6.91, N 3.56%
#20	$C_{19}H_{34}NO_2Cl$	C 66.35, H 9.96, N 4.07%	C 66.22, H 9.72, N 4.12%
#21	$C_{24}H_{32}NO_3Cl$	C 68.97, H 7.72, N 3.35%	C 67.52, H 7.99, N 3.17%
#22	$C_{17}H_{24}NO_2Cl_2 \cdot H_2O$	C 51.21, H 6.57, N 3.51%	C 51.03, H 6.57, N 3.36%
#23	$C_{17}H_{22}NO_2Cl_2$	C 53.91, H 5.86, N 3.70%	C 53.88, H 5.79, N 3.59%
#24	$C_{18}H_{26}NO_2Cl_3 \cdot H_2O$	C 52.38, H 6.84, N 3.39%	C 53.98, H 7.24, N 3.33%
#25	$C_{24}H_{30}NO_2Cl$	C 72.07, H 7.56, N 3.50%	C 71.87, H 7.57, N 3.51%
#26	$C_{17}H_{24}NOCl_3S$	C 51.46, H 6.10, N 3.53%	C 51.48, H 5.86, N 3.44%
#27	$C_{22}H_{28}NO_2Cl$	C 70.67, H 7.55, N 3.75%	C 70.63, H 7.53, N 3.65%

EXAMPLE 28

ASSESSMENT OF ANTIARRHYTHMIC EFFICACY

Antiarrhythmic efficacy was assessed by investigating the effect of a compound on the incidence of cardiac arrhythmias in conscious rats subject to coronary artery occlusion. Rats weighing 200-300 gms were subjected to preparative surgery and assigned to groups in a random block design. In each case, the animal was anesthetized with halothane during surgical preparation. The left femoral artery was cannulated for measurement of mean arterial blood pressure and withdrawal of blood samples. The left femoral vein was also cannulated for injection of drugs. The thoracic cavity was opened and a polyethylene occluder loosely placed around the left anterior descending coronary artery. The thoracic cavity was then closed. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All cannulae and electrode leads were exteriorized in the mid scapular region. In a random and double-blind manner, about 0.5 to 2 hours post-surgery, an infusion of vehicle, or the compound to be tested was given. After 15 minutes infusion, the occluder was pulled so as to produce coronary artery occlusion. ECG, arrhythmias, blood pressure, heart rate and mortality were monitored for 30 minutes after occlusion. Arrhythmias were recorded as ventricular tachycardia (VT) and ventricular fibrillation (VF) and scored according to Curtis, M.J. and Walker, M.J.A., *Cardiovasc. Res.* 22:656 (1988) (see Table 2).

Table 2

Score	Description
0	0-49 VPBs
1	50-499 VPBs
2	>499 VPBs and/or 1 episode of spontaneously reverting VT or VF
3	>1 episode of VT or VF or both (>60s total combined duration)
4	VT or VF or both (60-119s total combined duration)
5	VT or VF or both (> 119s total combined duration)
6	fatal VF starting at > 15 min after occlusion
7	fatal VF starting at between 4 min and 14 min 59s after occlusion
8	fatal VF starting at between 1 min and 3 min 59s after occlusion
9	fatal VF starting < 1 min after occlusion

Where: VPB = ventricular premature beats

VT = ventricular tachycardia

VF = ventricular fibrillation

Rats were excluded from the study if they did not exhibit pre-occlusion serum potassium concentrations within the range of 2.9-3.9 mM. Occlusion is associated with increases in R-wave height and "S-T" segment elevation; and an occluded zone (measured after death by cardiogreen dye perfusion) in the range of 25%-50% of total left-ventricular weight.

Table 3 describes the result of tests of the compounds described therein as values of a given infusion rate in micromol/kg/min. (ED₅₀AA) which will reduce the arrhythmia score in treated animals to 50% of that shown by animals treated only with the vehicle in which the test drug(s) is dissolved.

Table 3

Compound	ED ₅₀ AA
#1	0.8
#2	1.0
#3	2.1
#4	2.0
#5	3.0
#6	4.0
#7	4.0
#8	1.0
#9	1.0
#10	2.0
#11	1.0
#14	1.5
#15	0.43
#17	1.1
#19	1.4
#21	1.4
#22	1.8
#23	2.1
#24	0.6
#25	2.5
#26	6.5

EXAMPLE 29

MEASUREMENT OF ECG PARAMETERS

Rats weighing 200-250 gms were used in this example. Animals were anesthetized with 60 mg/kg pentobarbitone i.p. The carotid artery and jugular vein were cannulated for measurement of blood pressure and drug injection, respectively. ECG was recorded by insertion of electrodes placed along the anatomical axis of the heart. All compounds were given as bolus injections.

Various ECG parameters were measured. Table 4 describes the results of the tests as ED₂₅ (micromol/kg) which are the doses required to produce a 25% increase in the parameter measured (ne = not estimated). The increases in P-R interval and QRS interval indicate cardiac sodium channel blockage while the increase in Q-T interval indicates ancillary cardiac potassium channel blockage which is the property of a type 1a antiarrhythmic.

Table 4

Compound	PR	QRS	QT
#1	NE	NE	2.5
#2	5.6	8	2.0
#3	32	16	3.0
#6	NE	NE	NE
#7	1.1	1.5	0.9
#14	-	21.5	1.4
#15	15.8	7.8	3.4
#17	30	26	4.2
#21	1.7	2.3	1.6
#23	-	17.2	2.7
#24	1.4	1.6	1.0
#26	2.3	-	10

EXAMPLE 30

ASSESSMENT OF SODIUM CHANNEL BLOCKAGE

Rats were prepared according to the preceding procedure. Two silver stimulating electrodes were inserted through the chest wall and implanted in the left ventricle. Square wave stimulation was used to determine threshold current for capture, ventricular fibrillation threshold current, and effective refractory period (Howard, P.G. and Walker, M.J.A., *Proc. West. Pharmacol. Soc.* 33:123-127 (1990)). Table 5 contains ED₂₅ values for these indices of cardiac sodium channel blockage, where the ED₂₅ is the infusion rate in micromol/kg/minute of compound required to elicit a 25% increase from control. The increases in refractoriness indicate ancillary blockage of potassium channels. The threshold current for capture is represented by "It". The fibrillation threshold current is represented by "VFT". The effective refracting period is represented by "ERP".

Table 5

Compound	It	VFT	ERP
#1	2.8	1.4	1.5
#2	0.9	0.7	1.3
#3	5.8	NE	4.0
#7	0.7	0.2	0.4
#14	6.4	-	1.7
#15	5	1.2	1.6
#17	6	7.3	7.1
#23	7.6	6.2	5
#24	1.7	1.2	1.1
#26	10.5	9	5.4

EXAMPLE 31

CANINE VAGAL-AF MODEL

General methods

Mongrel dogs of either sex weighing 15-49 kg were anesthetized with morphine (2 mg/kg im initially, followed by 0.5 mg/kg IV every 2 h) and α -chloralose (120 mg/kg IV followed by an infusion of 29.25 mg/kg/h; St.-Georges et al., 1997).

Dogs were ventilated mechanically with room air supplemented with oxygen via an endotracheal tube at 20 to 25 breaths/minute with a tidal volume obtained from a nomogram. Arterial blood gases were measured and kept in the physiological range ($\text{SAO}_2 > 90\%$, pH 7.30-7.45). Catheters were inserted into the femoral artery for blood
5 pressure recording and blood gas measurement, and into both femoral veins for drug administration and venous sampling. Catheters were kept patent with heparinized 0.9% saline solution. Body temperature was maintained at 37-40°C with a heating blanket.

The heart was exposed via a medial thoracotomy and a pericardial cradle was created. Three bipolar stainless steel, Teflon™-coated electrodes were inserted into
10 the right atria for recording and stimulation, and one was inserted into the left atrial appendage for recording. A programmable stimulator (Digital Cardiovascular Instruments, Berkeley, CA) was used to stimulate the right atrium with 2 ms, twice diastolic threshold pulses. Two stainless steel, Teflon™-coated electrodes were inserted into the left ventricle, one for recording and the other for stimulation. A ventricular
15 demand pacemaker (GBM 5880, Medtronic, Minneapolis, MN) was used to stimulate the ventricles at 90 beats/minute when (particular during vagal-AF) the ventricular rate became excessively slow. A P23 ID transducer, electrophysiological amplifier (Bloom Associates, Flying Hills, PA) and paper recorder (Astromed MT-95000, Toronto, ON, Canada) were used to record ECG leads II and III, atrial and ventricular electrograms,
20 blood pressure and stimulation artefacts. The vagi were isolated in the neck, doubly-ligated and divided, and electrodes inserted in each nerve (see below). To block changes in β -adrenergic effects on the heart, nadolol was administered as an initial dose of 0.5 mg/kg iv, followed by 0.25 mg/kg IV every two hours.

Atrial fibrillation model

25 Drug effects to terminate sustained AF maintained during continuous vagal nerve stimulation were assessed. Unipolar hook electrodes (stainless steel insulated with Teflon™, coated except for the distal 1-2 cm) were inserted via a 21 gauge needle within and parallel to the shaft of each nerve. In most experiments, unipolar stimuli were applied with a stimulator (model DS-9F, Grass Instruments,

Quincy, MA) set to deliver 0.1 ms square-wave pulses at 10 Hz and a voltage 60% of that required to produce asystole. In some experiments, bipolar stimulation was used. The voltage required to produce asystole ranged between 3-20 volts. Under control conditions, a short burst of rapid atrial pacing (10 Hz, four times diastolic threshold) was delivered to induce AF which was ordinarily sustained for more than 20 minutes. The vagal stimulation voltage was adjusted under control conditions, and then readjusted after each treatment to maintain the same bradycardic effect. AF was defined as rapid (>500 minute under control conditions), irregular atrial rhythm with varying electrogram morphology.

10 Measurement of electrophysiological variables and vagal response

Diastolic threshold current was determined at a basic cycle length of 300 ms by increasing the current 0.1 mA incrementally until stable capture was obtained. For subsequent protocols current was set to twice diastolic threshold. Atrial and ventricular ERP was measured with the extrastimulus method, over a range of S1S2 intervals at a basic cycle length of 300 ms. A premature extrastimulus S2 was introduced every 15 basic stimuli. The S1S2 interval was increased in 5 ms increments until capture occurred, with the longest S1S2 interval consistently failing to produce a propagated response defining ERP. Diastolic threshold and ERP were determined in duplicate and averaged to give a single value. These values were generally within 5 ms. The interval between the stimulus artefact and the peak of the local electrogram was measured as an index of conduction velocity. AF cycle length (AFCL) was measured during vagal-AF by counting the number of cycles (number of beats -1) over a 2-second interval at each of the atrial recording sites. The three AFCLs measurements were averaged to obtain an overall mean AFCL for each experimental condition.

25 The stimulus voltage-heart rate relationship for vagal nerve stimulation was determined under control conditions in most experiments. The vagal nerves were stimulated as described above with various voltages to determine the voltage which caused asystole (defined as a sinus pause greater than 3 seconds). The response to vagal nerve stimulation was confirmed under each experimental condition and the voltage

adjusted to maintain the heart rate response to vagal nerve stimulation constant. In cases in which it was not possible to produce asystole, vagal nerve stimulation was adjusted to a voltage which allowed two 20-minute episodes of vagal-AF to be maintained under control conditions (see below).

5 Experimental protocols

The experimental groups studied are summarized in Table 5. Each dog received only one drug at doses indicated in Table 5. The first series of experiments were dose ranging studies, followed by blinded study in which 1-3 doses were given. All drugs were administered IV via an infusion pump, with drug solutions prepared
10 freshly in plastic containers on the day of the experiment. Vagal stimulation parameters were defined under control conditions as described above, and maintenance of AF during 20 minutes of vagal nerve stimulation under control conditions was verified. After the termination of AF, the diastolic threshold and ERP of the atrium and ventricle were determined. Subsequently, these variables were reassessed in the atrium under
15 vagal nerve stimulation. Electrophysiological testing usually took 15-20 minutes. The heart rate response to vagal nerve stimulation was confirmed and the vagal-AF/electrophysiological testing protocol was repeated. A pre-drug blood sample was obtained and vagal-AF reinstituted. Five minutes later, one of the treatments was administered at doses shown in Table 5. The total dose was infused over 5 minutes and
20 a blood sample obtained immediately thereafter. No maintenance infusion was given. If AF terminated within 15 minutes, the electrophysiological measurements obtained under control conditions were repeated and a blood sample was obtained. If AF was not terminated by the first dose (within 15 minutes), a blood sample was obtained and vagal stimulation was discontinued to allow a return to sinus rhythm. The
25 electrophysiological measurements were repeated and a third and final blood sample for this dose was obtained. AF was reinitiated and the vagal-AF/drug infusion/electrophysiological testing protocol was repeated until AF was terminated by the drug.

Statistical analysis

Group data are expressed as the mean \pm SEM. Statistical analysis was carried out for effective doses for AFCL, and ERP using a t-test with a Bonferroini correction for multiple comparisons. Drug effects on blood pressure, heart rate, diastolic threshold and ECG intervals were assessed at the median dose for termination of AF. Two tailed tests were used and a $p < 0.05$ was taken to indicate statistical significance.

Table 6

EXPERIMENTAL GROUPS AND DOSES OF DRUGS

Drug	Dose range tested (μ mol/kg)	Effective doses for terminating AF (μ mol/kg)	Mean dose required for termination of AF (μ mol/kg)	Median dose required for termination of AF (μ mol/kg)
Flecainide	1.25-10	4-2.5; 1-10	4 ± 2	2.5

A single drug was administered to each dog over the dose range specified until AF was terminated. The number of dogs in which AF was terminated at each dose is shown (number of dogs-dose, in μ mol/kg). The mean \pm SEM as well as the median dose required to terminate AF is shown. Each dog received only one drug.

A number of the compounds of the present invention have been evaluated by this method. The results showed that all of the compounds tested are effective in terminating AF in the canine vagal-AF model. The conversion rates are similar to those reported for a variety of other class I and III drugs in this model. The effectiveness of flecainide as a control in the present study was comparable to that previously reported. All of the drugs prolonged AFCL prior to termination of AF; effects which are globally consistent with the wave length of re-entry model for termination of AF. The tested compounds of the present invention did not reduce blood pressure or heart rate at the median dose for termination of vagal-AF. The heart rate response to vagal nerve stimulation was similar in all groups and was not influenced by

any of the compounds tested. Vagal nerve stimulation at 60% of the voltage required to produce asystole (10 ± 1 V) produced a 1.3 ± 0.1 second pause.

EXAMPLE 32

5

CANINE STERILE PERICARDITIS MODEL

This model has been used to characterize the mechanisms of AF and atrial flutter (AFL). Waldo and colleagues have found that AF depends on reentry and that the site of termination is usually an area of slowed conduction. This canine model is prepared by dusting the exposed atria with talcum powder followed by "burst" pacing the atria over a period of days after recovery. AF is inducible two days after surgery, however, by the fourth day after surgical preparation; sustainable atrial flutter is the predominant inducible rhythm. The inducibility of AF at day 2 is somewhat variable, such that only 50% of dogs may have sustained AF (generally <60 minutes) for a requisite of 30 minutes. However, the sustainable atrial flutter that evolves by the fourth day is inducible in most preparations. Atrial flutter is more readily "mapped" for purposes of determining drug mechanisms. Inducibility of AF subsides after the fourth day post-surgery, similar to the AF that often develops following cardiac surgery that the sterile pericarditis model mimics. There may be an inflammatory component involved in the etiology of post-surgery AF that would provide a degree of selectivity to an ischaemia or acid selective drug. Similarly, while coronary artery bypass graft (CABG) surgery is performed to alleviate ventricular ischaemia, such patients may also be at risk for mild atrial ischaemia due to coronary artery disease (CAD). While atrial infarcts are rare, there has been an association between AV nodal artery stenosis and risk for AF following CABG surgery. Surgical disruption of the autonomic innervation of the atria may also play a role in AF following CABG.

Methods

Studies were carried out in a canine model of sterile pericarditis to determine the potency and efficacy of Compound 1 in terminating atrial

fibrillation/flutter. Atrial flutter or fibrillation was induced 2 to 4 days after creation of sterile pericarditis in adult mongrel dogs weighing 19 kg to 25 kg. In all instances, the atrial fibrillation or flutter lasted longer than 10 minutes. All studies were performed in accordance with guidelines specified by our Institutional Animal Care and Use Committee, the American Heart Association Policy on Research Animal Use, and the Public Health Service Policy on Use of Laboratory Animals.

Creation of the Sterile Pericarditis Atrial Fib/Flutter Model

The canine sterile pericarditis model was created as previously described. At the time of surgery, a pair of stainless steel wire electrodes coated with FEP polymer except for the tip (O Flexon, Davis and Geck) were sutured on the right atrial appendage, Bachman's bundle and the posteroinferior left atrium close to the proximal portion of the coronary sinus. The distance between each electrode of each pair was approximately 5 mm. These wire electrodes were brought out through the chest wall and exteriorized posteriorly in the interscapular region for subsequent use. At the completion of surgery, the dogs were given antibiotics and analgesics and then were allowed to recover. Postoperative care included administration of antibiotics and analgesics.

In all dogs, beginning on postoperative day 2, induction of stable atrial fibrillation/flutter was attempted in the conscious, non-sedated state to confirm the inducibility and the stability of atrial fib/flutter and to test the efficacy of the drugs. Atrial pacing was performed through the electrodes sutured during the initial surgery. On postoperative day 4, when stable atrial flutter was induced, the open-chest study was performed.

For the open-chest study, each dog was anesthetized with pentobarbital (30 mg/kg IV) and mechanically ventilated with 100% oxygen by use of a Boyle model 50 anesthesia machine (Harris-Lake, Inc.). The body temperature of each dog was kept within the normal physiological range throughout the study with a heating pad. With the dog anesthetized, but before the chest was opened, radiofrequency ablation of the His bundle was performed to create complete atrioventricular (AV) block by standard

electrode catheter techniques. This was done to minimize the superimposition of atrial and ventricular complexes during subsequent recordings of unipolar atrial electrograms after induction of atrial flutter. After complete AV block was created, an effective ventricular rate was maintained by pacing of the ventricles at a rate of 60 to 80 beats per minute with a Medtronic 5375 Pulse Generator (Medtronic Inc.) to deliver stimuli via the electrodes sutured to the right ventricle during the initial surgery.

Determination of Stimulus Thresholds and Refractory Periods During Pacing

For the induction of AF/AFL, one of two previously described methods was used: (1) introduction of one or two premature atrial beats after a train of 8 paced atrial beats at a cycle length of 400 ms, 300 ms, 200 ms, or 150 ms, or (2) rapid atrial pacing for periods of 1 to 10 seconds at rates incrementally faster by 10 to 50 beats per minute than the spontaneous sinus rate until atrial flutter was induced or there was a loss of 1:1 atrial capture. Atrial pacing was performed from either the right atrial appendage electrodes or the posteroinferior left atrial electrodes. All pacing was performed using stimuli of twice threshold for each basic drive train with a modified Medtronic 5325 programmable, battery-powered stimulator with a pulse width of 1.8 ms.

After the induction of stable atrial fib/flutter (lasting longer than 10 minutes), the atrial fib/flutter cycle length was measured and the initial mapping and analysis were performed to determine the location of the atrial fib/flutter reentrant circuit. Atrial flutter was defined as a rapid atrial rhythm (rate, >240 beats per minute) characterized by a constant beat-to-beat cycle length, polarity, morphology, and amplitude of the recorded bipolar electrograms.

Drug Efficacy Testing Protocol

1. Effective refractory periods (ERPs) were measured from three sites: right atrial appendage (RAA), posterior left atrium (PLA), and Bachman's Bundle (BB), at two basic cycle lengths 200 and 400 ms.

2. Pace induce A-Fib or AFL. This was attempted for one hour. If no arrhythmia was induced, no further study was done on that day.

3. If induced, AF must have been sustained for 10 minutes. Then a waiting period was allowed for spontaneous termination or 20 minutes, whichever came first.

4. AF was then reinduced and 5 minutes was allowed before starting drug infusion.

5. Drug was then infused in a bolus over 5 minutes.

6. If AF terminated with the first dose then a blood sample was taken and ERP measurements were repeated.

7. Five minutes was allowed for the drug to terminate. If there was no termination then the second dose was given over 5 minutes.

8. After termination and ERPs were measured, a second attempt to reinduce AF was tried for a period of ten minutes.

9. If reinduced and sustained for 10 minutes, a blood sample was taken and the study repeated from #3 above.

10. If no reinduction, then the study was over.

EXAMPLE 33

ASSESSMENT OF PAIN BLOCKAGE

5 Guinea pigs were shaved (backs only) and 6 aliquots (50 μ l) of compound solution (10 mg/ml) were injected just beneath the skin to form 6 blebs which were outlined with a permanent marker. Pain responses were assessed as above on each bleb at regular intervals up to 4 hours post injection and the duration of pain blockage was recorded for three animals for each test solution.

Table 7

Compound	Duration of Blockage (hours)
1	2.5
2	3
3	2.5
11	3
Saline	0

10

A number of the compounds of the present invention have been evaluated by this method. The results showed that all of the compounds tested are effective in terminating episodes of atrial fibrillation/flutter in this model. There was no proarrhythmia or cardiovascular adverse events observed during drug treatment.

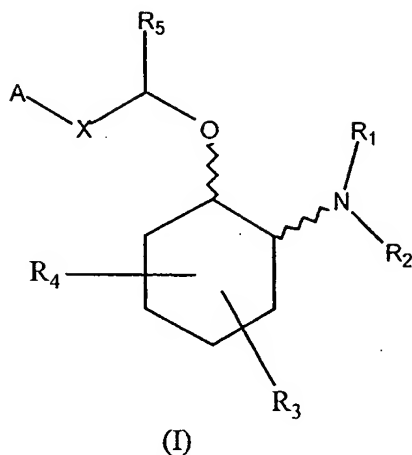
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All publications and patent applications mentioned in this specification are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually incorporated by reference.

20 From the foregoing it will be appreciated that, although specific embodiments of the invention have been described herein for purposes of illustration, various modifications may be made without deviating from the spirit and scope of the invention. Accordingly, the invention is not limited except as by the appended claims.

CLAIMS

1. A compound of formula (I), or a solvate or pharmaceutically acceptable salt thereof:



wherein, independently at each occurrence,

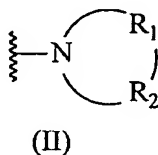
X is selected from a direct bond, $-C(R_6, R_{14})-Y-$, and $-C(R_{13})=CH-$;

Y is selected from a direct bond, O, S, and C_1-C_4 alkylene;

R_{13} is selected from hydrogen, C_1-C_6 alkyl, C_3-C_8 cycloalkyl, aryl, and benzyl;

R_1 and R_2 are independently selected from hydrogen, C_1-C_8 alkyl, C_3-C_8 alkoxyalkyl, C_1-C_8 hydroxyalkyl, and C_7-C_{12} aralkyl; or

R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (I), form a ring denoted by formula (II):



wherein the ring of formula (II) is formed from the nitrogen as shown as well as three to nine additional ring atoms independently selected from carbon, nitrogen, oxygen, and sulfur; where any two adjacent ring atoms may be joined together by single or double bonds, and where any one or more of the additional carbon ring atoms may be substituted with one or two substituents selected from hydrogen, hydroxy, C_1-C_3 hydroxyalkyl, oxo, C_2-C_4 acyl,

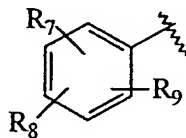
C_1 - C_3 alkyl, C_2 - C_4 alkylcarboxy, C_1 - C_3 alkoxy, C_1 - C_{20} alkanoyloxy, or may be substituted to form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur; and any two adjacent additional carbon ring atoms may be fused to a C_3 - C_8 carbocyclic ring, and any one or more of the additional nitrogen ring atoms may be substituted with substituents selected from hydrogen, C_1 - C_6 alkyl, C_2 - C_4 acyl, C_2 - C_4 hydroxyalkyl and C_3 - C_8 alkoxyalkyl; or

R_1 and R_2 , when taken together with the nitrogen atom to which they are directly attached in formula (I), may form a bicyclic ring system selected from 3-azabicyclo[3.2.2]nonan-3-yl, 2-azabicyclo[2.2.2]octan-2-yl, 3-azabicyclo[3.1.0]hexan-3-yl, and 3-azabicyclo[3.2.0]heptan-3-yl;

R_3 and R_4 are independently attached to the cyclohexane ring shown in formula (I) at the 3-, 4-, 5- or 6- positions and are independently selected from hydrogen, hydroxy, C_1 - C_6 alkyl, and C_1 - C_6 alkoxy, and, when both R_3 and R_4 are attached to the same cyclohexane ring atom, may together form a spiro five- or six-membered heterocyclic ring containing one or two heteroatoms selected from oxygen and sulfur;

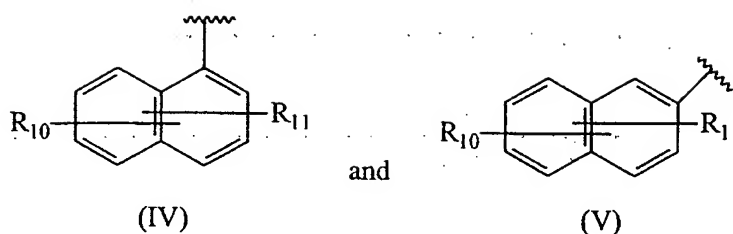
R_5 , R_6 and R_{14} are independently selected from hydrogen, C_1 - C_6 alkyl, aryl and benzyl, or R_6 and R_{14} , when taken together with the carbon to which they are attached, may form a spiro C_3 - C_5 cycloalkyl;

A is selected from C_5 - C_{12} alkyl, a C_3 - C_{13} carbocyclic ring, and ring systems selected from formulae (III), (IV), (V), (VI), (VII) and (VIII):

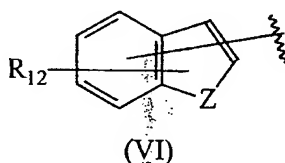


(III)

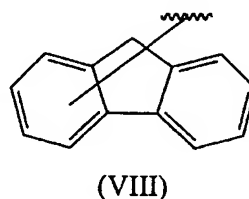
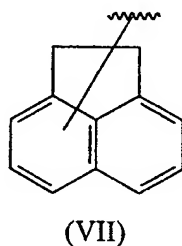
where R_7 , R_8 and R_9 are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, aryl and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl;



where R_{10} and R_{11} are independently selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl;

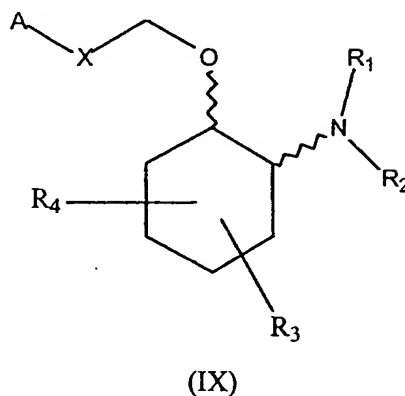


where R_{12} is selected from bromine, chlorine, fluorine, carboxy, hydrogen, hydroxy, hydroxymethyl, methanesulfonamido, nitro, sulfamyl, trifluoromethyl, C_2 - C_7 alkanoyloxy, C_1 - C_6 alkyl, C_1 - C_6 alkoxy, C_2 - C_7 alkoxycarbonyl, C_1 - C_6 thioalkyl, and $N(R_{15}, R_{16})$ where R_{15} and R_{16} are independently selected from hydrogen, acetyl, methanesulfonyl, and C_1 - C_6 alkyl; and Z is selected from CH, CH_2 , O, N and S, where Z may be directly bonded to "X" as shown in formula (I) when Z is CH or N, or Z may be directly bonded to R_{17} when Z is N, and R_{17} is selected from hydrogen, C_1 - C_6 alkyl, C_3 - C_8 cycloalkyl, aryl and benzyl;



including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

2. A compound according to claim 1 having formula (IX), or a solvate or pharmaceutically acceptable salt thereof:



wherein, independently at each occurrence,

X is selected from a direct bond, -CH=CH- and -C(R₆,R₁₄)-Y-;

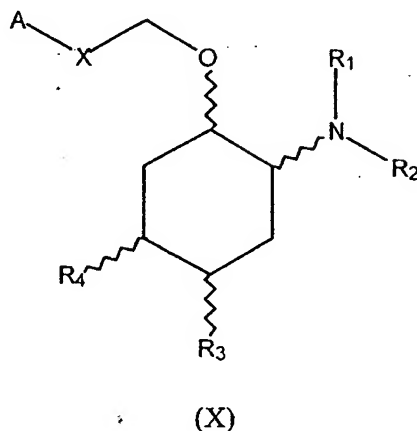
Y is selected from a direct bond, O and S; and

R₁, R₂, R₃, R₄, R₆, R₇, R₈, R₉, R₁₀, R₁₁, R₁₂, R₁₄, A and Z are defined as in claim 1;

including isolated enantiomeric, diastereomeric and geometric isomers thereof,

and mixtures thereof.

3. A compound of claim 1 having formula (X), or a solvate or pharmaceutically acceptable salt thereof:



wherein, independently at each occurrence,

X is selected from a direct bond, $-\text{CH}=\text{CH}-$ and $-\text{C}(\text{R}_6, \text{R}_{14})-\text{Y}-$;

Y is selected from a direct bond, O, and S;

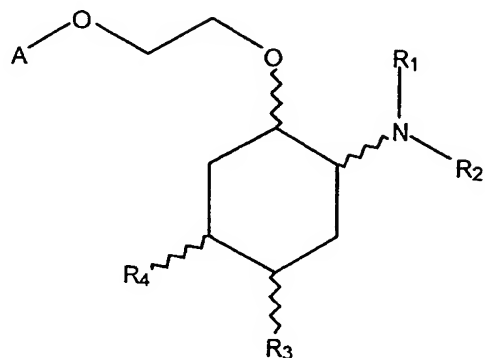
R_1 , R_2 , R_6 and R_{14} are defined as in claim 1;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and C_1 - C_6 alkoxy; and

A is selected from C_5 - C_{12} alkyl, C_3 - C_8 cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as defined in claim 1, wherein Z, R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} are defined as in claim 1;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

4. A compound of claim 1 having formula (XI), or a solvate or pharmaceutically acceptable salt thereof:



(XI)

wherein, independently at each occurrence,

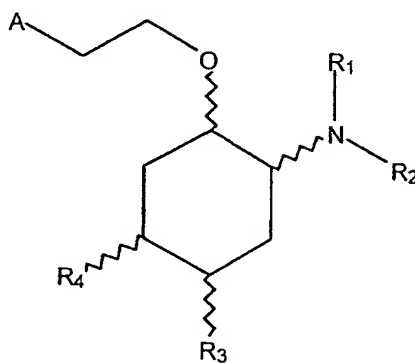
R_1 and R_2 are defined as in claim 1;

R_3 and R_4 are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C_5 - C_{12} alkyl, C_3 - C_8 cycloalkyl, and any of formulae (III), (IV), (V), and (VI) as defined in claim 1, wherein Z, R_7 , R_8 , R_9 , R_{10} , R_{11} and R_{12} are defined as in claim 1;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

5. A compound of claim 1 having formula (XII), or a solvate or pharmaceutically acceptable salt thereof:



(XII)

wherein, independently at each occurrence,

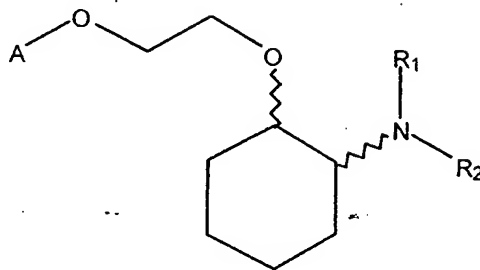
R₁ and R₂ are defined as in claim 1;

R₃ and R₄ are independently attached to the cyclohexane ring at the 4- or 5-positions, and are independently selected from hydrogen and methoxy; and

A is selected from C₅-C₁₂alkyl, C₃-C₈cycloalkyl, and any of formulae (III), (IV), (V) and (VI) as defined in claim 1, wherein Z, R₇, R₈, R₉, R₁₀, R₁₁ and R₁₂ are defined as in claim 1;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

7. A compound of claim 1 having formula (XIV), or a solvate or pharmaceutically acceptable salt thereof:



(XIV)

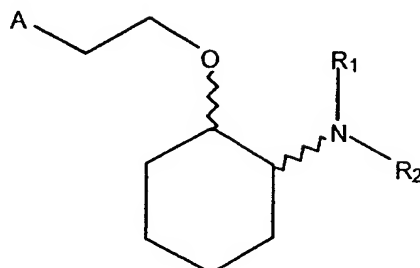
wherein, independently at each occurrence,

R_1 and R_2 are defined as in claim 1; and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined in claim 1, wherein R_7 , R_{10} , R_{11} and R_{12} are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2 , with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

8. A compound of claim 1 having formula (XV); or a solvate or pharmaceutically acceptable salt thereof:



(XV)

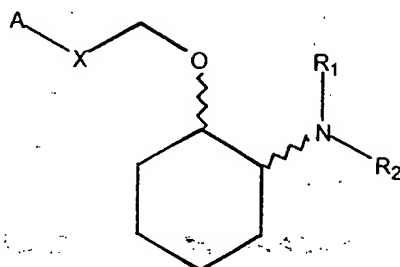
wherein, independently at each occurrence,

R_1 and R_2 are defined as in claim 1; and

A is selected from any of formulae (III), (IV), (V) and (VI) as defined in claim 1, wherein R_7 , R_{10} , R_{11} and R_{12} are hydrogen, R_8 and R_9 are independently selected from hydrogen, hydroxy, fluorine, chlorine, bromine, methanesulfonamido, methanoyloxy, methoxycarbonyl, nitro, sulfamyl, thiomethyl, trifluoromethyl, methyl, ethyl, methoxy, ethoxy and NH_2 , with the proviso that at least one of R_8 and R_9 is not hydrogen; and Z is selected from O and S;

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

9. A compound of claim 1 having formula (XVI), or a solvate or pharmaceutically acceptable salt thereof:



(XVI)

wherein, independently at each occurrence,

X is selected from a direct bond, *trans*-CH=CH-, -CH₂- and -CH₂-O-;

R₁ and R₂ are both methoxyethyl or, when taken together with the nitrogen atom to which they are attached, complete a ring selected from pyrrolidinyl, ketopyrrolidinyl, acetoxypyrrolidinyl, hydroxypyrrolidinyl, thiazolidinyl, piperidinyl, ketopiperidinyl, acetylpiperazinyl, 1,4-dioxo-7-azaspiro[4.4]non-7-yl, hexahydroazepinyl, morpholinyl, N-methylpiperazinyl and 3-azabicyclo[3.2.2]nonanyl; and

A is selected from cyclohexyl, monochlorophenyl, 2,6-dichlorophenyl, 3,4-dichlorophenyl, 2-bromophenyl, 2,4-dibromophenyl, 3-bromophenyl, 4-bromophenyl, 1-naphthyl, 2-naphthyl, 3-benzo(b)thiophenyl, 4-benzo(b)thiophenyl, (2-trifluoromethyl)phenyl, 2,4-di(trifluoromethyl)phenyl, and (4-trifluoromethyl)phenyl.

including isolated enantiomeric, diastereomeric and geometric isomers thereof, and mixtures thereof.

10. A compound, or mixture comprising compounds, selected from the group consisting of:

- (+)-*trans*-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(2-naphthenethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(1-naphthenethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(4-bromophenethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy]]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-[2-(2-naphthoxy)ethoxy]]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-[2-(4-bromophenoxy)ethoxy]]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(3,4-dimethoxyphenethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(3,4-dimethoxyphenethoxy)]cyclohexane;
- (+)-*trans*-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane;
- (-)-*trans*-[2-(1-pyrrolidinyl)-1-(1-naphthenethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl)ethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-3-yl)ethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl)ethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(2-(benzo[b]thiophen-4-yl)ethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(3-bromophenethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(2-bromophenethoxy)]cyclohexane;
- (+)-*trans*-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)-1-propoxy)]cyclohexane;
- (-)-*trans*-[2-(4-morpholinyl)-1-(3-(3,4-dimethoxyphenyl)-1-propoxy)]cyclohexane;
- (+)-*trans*-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane;
- (-)-*trans*-[2-[bis(2-methoxyethyl)aminyl]-1-(2-naphthenethoxy)]cyclohexane;
- (1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-(3,4-dichlorophenethoxy)cyclohexane;
- (1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane;

(1R,2R)/(1S,2S)-2-(1-acetylpiperazinyl)-1-(2-naphthenethoxy)cyclohexane;
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane;
(1R,2R)/(1S,2S)-2-[1,4-dioxo-7-azaspiro[4.4]non-7-yl]-1-(1-naphthenethoxy)cyclohexane;
(1R,2S)/(1S,2R)-2-(4-morpholinyl)-1-[(2-trifluoromethyl)phenethoxy]cyclohexane;
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[3-(cyclohexyl)propoxy]cyclohexane;
(1R,2R)/(1S,2S)-2-(3-acetoxypyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane;
(1R,2R)/(1S,2S)-2-(4-morpholinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane;
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-[(2,6-dichlorophenyl)methoxy]cyclohexane;
(1R,2R)/(1S,2S)-2-(3-hydroxypyrrolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane;
(1R,2R)/(1S,2S)-2-(3-ketopyrrolidinyl)-1-(2,2-diphenylethoxy)cyclohexane;
(1R,2R)/(1S,2S)-2-(3-yliazolidinyl)-1-(2,6-dichlorophenethoxy)cyclohexane; and
(1R,2S)/(1S,2R)-2-(3-ketopyrrolidinyl)-1-(1-naphthenethoxy)cyclohexane;
and pharmaceutically acceptable salts thereof.

11. A composition comprising a compound according to any one of claims 1-10 in combination with a pharmaceutically acceptable carrier, excipient or diluent.

12. Use of a compound according to any one of claims 1-10 in a manufacture of a medicament.

13. A compound or composition according to any one of claims 1-11 for use in a method for treating or preventing arrhythmia in a warm-blooded animal.

14. A compound or composition according to any one of claims 1-11 for use in a method for modulating ion channel activity in a warm-blooded animal.

15. A compound or composition according to any one of claims 1-11 for use in a method for modulating ion channel activity *in vitro*.

16. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent diseases of the central nervous system in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

17. A method for treating or preventing diseases of the central nervous system in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 16.

18. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent convulsion in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

19. A method for treating or preventing convulsion in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 18.

20. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent epileptic spasms in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

21. A method for treating or preventing epileptic spasms in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 20.

22. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent depression, anxiety or schizophrenia, in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

23. A method for treating or preventing depression, anxiety or schizophrenia, in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 22.

24. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent Parkinson's disease in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

25. A method for treating or preventing Parkinson's disease in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 24.

26. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent respiratory disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

27. A method for treating or preventing respiratory disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 26.

28. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent cystic fibrosis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

29. A method for treating or preventing cystic fibrosis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 28.

30. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent asthma in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

31. A method for treating or preventing asthma in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 30.

32. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent a cough in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

33. A method for treating or preventing a cough in a warm-blooded animal comprising administration of a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 32.

34. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent inflammation in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

35. A method for treating or preventing inflammation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 34.

36. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent arthritis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

37. A method for treating or preventing arthritis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 36.

38. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent allergies in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

39. A method for treating or preventing allergies in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 38.

40. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent gastrointestinal disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

41. A method for treating or preventing gastrointestinal disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 40.

42. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent urinary incontinence in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

43. A method for treating or preventing urinary incontinence in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 42.

44. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent irritable bowel syndrome in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

45. A method for treating or preventing irritable bowel syndrome in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 44.

46. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent cardiovascular diseases in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

47. A method for treating or preventing cardiovascular diseases in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 46.

48. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent cerebral or myocardial ischemias in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

49. A method for treating or preventing cerebral or myocardial ischemias in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 48.

50. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent hypertension in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

51. A method for treating or preventing hypertension in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 50.

52. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent long-QT syndrome in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

53. A method for treating or preventing long-QT syndrome in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 52.

54. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent stroke in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

55. A method for treating or preventing stroke in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 54.

56. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent migraine in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

57. A method for treating or preventing migraine in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 56.

58. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent ophthalmic diseases in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

59. A method for treating or preventing ophthalmic diseases in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 58.

60. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent diabetes mellitus in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

61. A method for treating or preventing diabetes mellitus in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 60.

62. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent myopathies in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

63. A method for treating or preventing myopathies in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 62.

64. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent Becker's myotonia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

65. A method for treating or preventing Becker's myotonia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 64.

66. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent myasthenia gravis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

67. A method for treating or preventing myasthenia gravis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 66.

68. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent paramyotonia congenita in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

69. A method for treating or preventing paramyotonia congenita in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 68.

70. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent malignant hyperthermia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

71. A method for treating or preventing malignant hyperthermia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 70.

72. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent hyperkalemic periodic paralysis in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

73. A method for treating or preventing hyperkalemic periodic paralysis in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 72.

74. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent Thomsen's myotonia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

75. A method for treating or preventing Thomsen's myotonia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 74.

76. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent autoimmune disorders in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

77. A method for treating or preventing autoimmune disorders in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 76.

78. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent graft rejection in organ transplantation or bone marrow transplantation in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

79. A method for treating or preventing graft rejection in organ transplantation or bone marrow transplantation in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 78.

80. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to produce local analgesia or anesthesia in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

81. A method for producing local analgesia or anesthesia in a warm-blooded animal in need thereof comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 80.

82. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent heart failure in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

83. A method for treating or preventing heart failure in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 82.

84. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent hypotension in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

85. A method for treating or preventing hypotension in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 84.

86. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent Alzheimer's disease in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

87. A method for treating or preventing Alzheimer's disease in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 86.

88. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent dementia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

89. A method for treating or preventing dementia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 88.

90. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to treat or prevent alopecia in a warm-blooded animal in need of the treatment or prevention, and a pharmaceutically acceptable carrier, diluent, or excipient.

91. A method for treating or preventing alopecia in a warm-blooded animal comprising administering to a warm-blooded animal in need thereof a therapeutically effective amount of a compound according to any one of claims 1-10 or a composition according to claim 90.

92. A pharmaceutical composition comprising an amount of a compound according to any one of claims 1-10 effective to enhance libido in a warm-blooded animal in need thereof, and a pharmaceutically acceptable carrier, diluent, or excipient.

93. A method for enhancing libido in a warm-blooded animal in need thereof comprising administering to a warm-blooded animal in need thereof an enhancing amount of a compound according to any one of claims 1-10 or a composition according to claim 92.

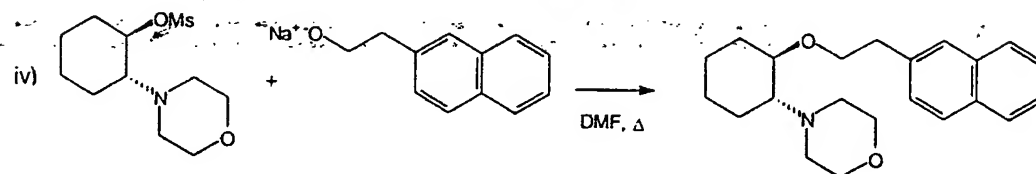
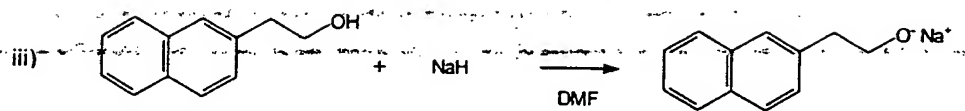
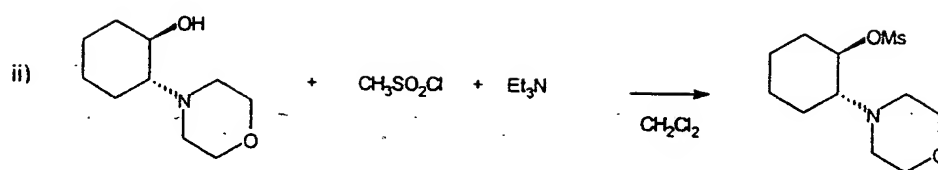
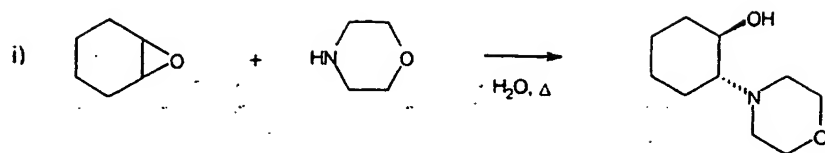
94. A compound or composition according to any one of claims 1-11 for use in a method for treating or preventing atrial arrhythmia in a warm-blooded animal.

95. A compound or composition according to any one of claims 1-11 for use in a method for treating or preventing ventricular arrhythmia in a warm-blooded animal.

96. A compound or composition according to any one of claims 1-11 for use in a method for treating or preventing atrial fibrillation in a warm-blooded animal.

97. A compound or composition according to any one of claims 1-11 for use in a method for treating or preventing ventricular fibrillation in a warm-blooded animal.

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**FIG. 1**

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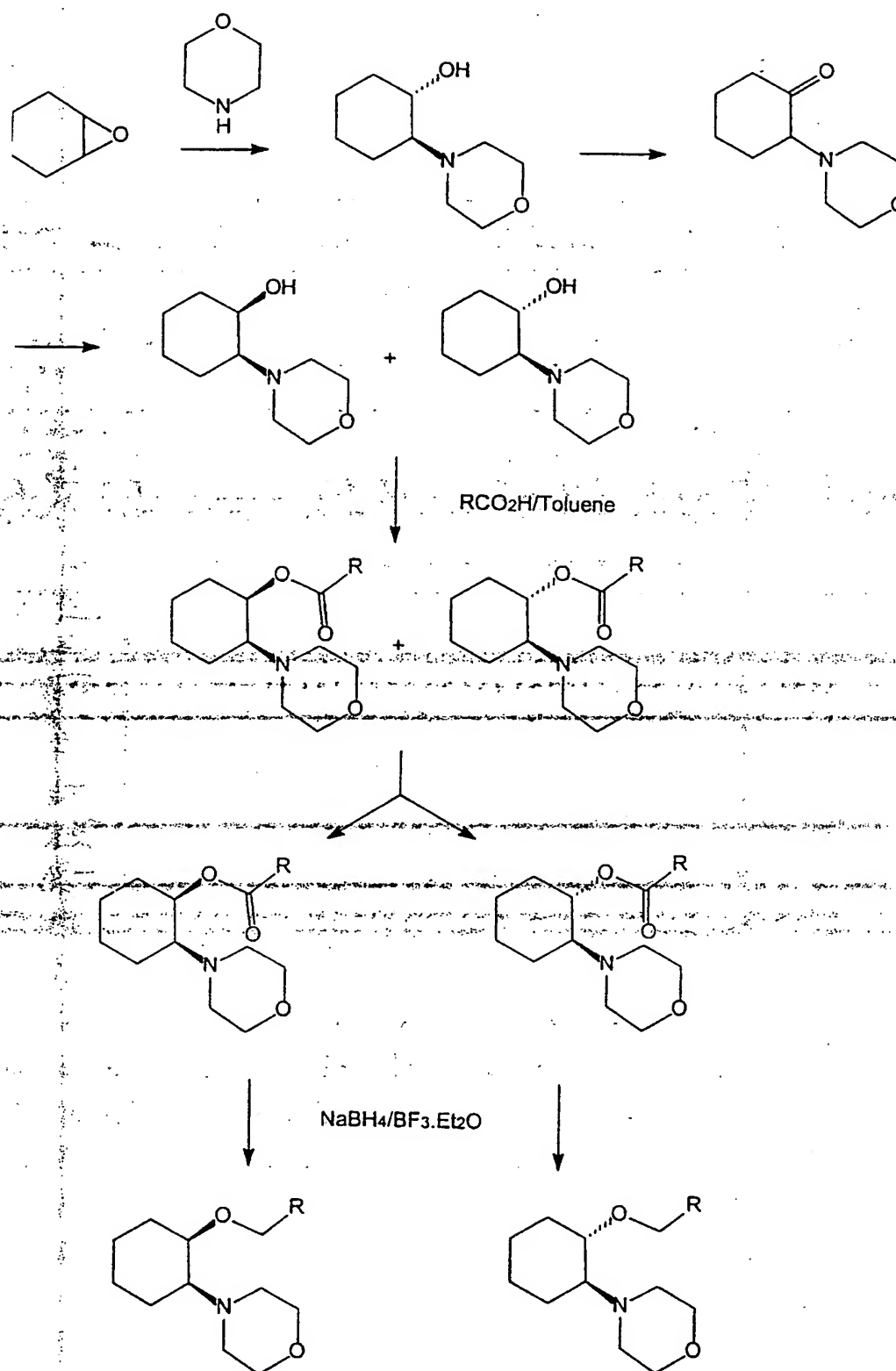
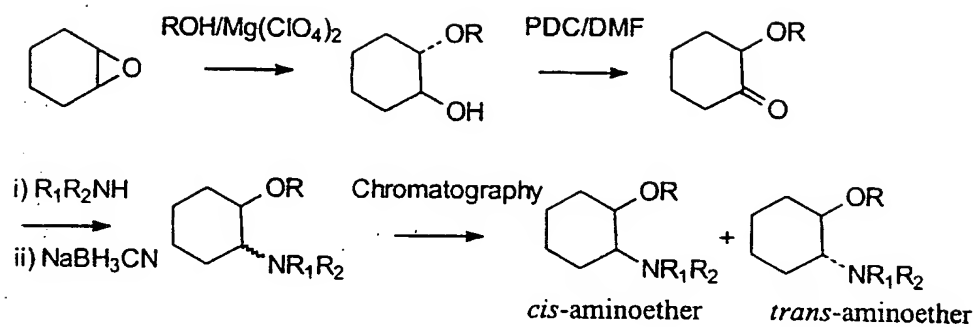
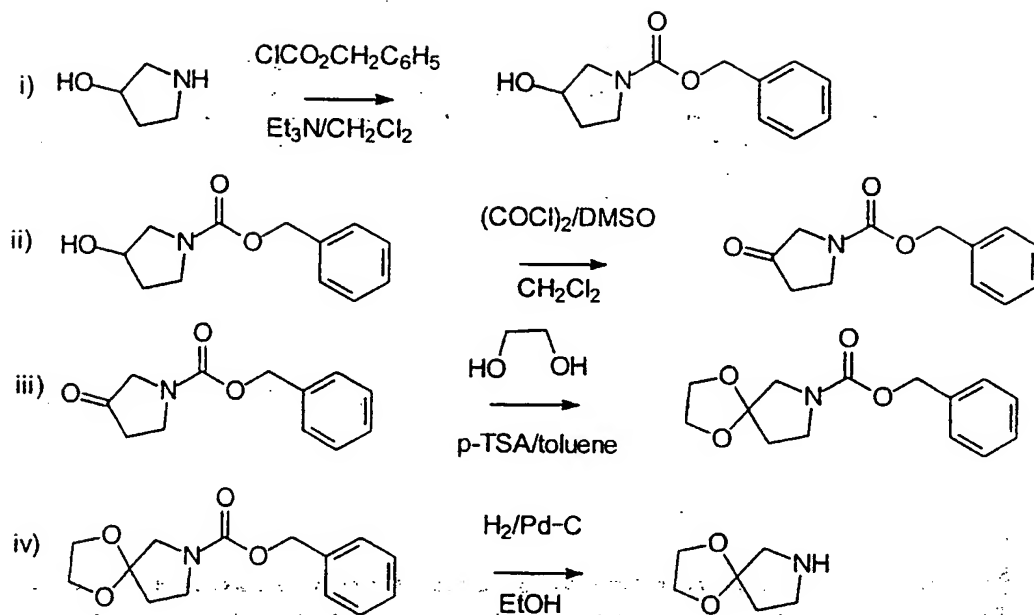


FIG. 2

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**FIG. 3**

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**FIG. 4A**

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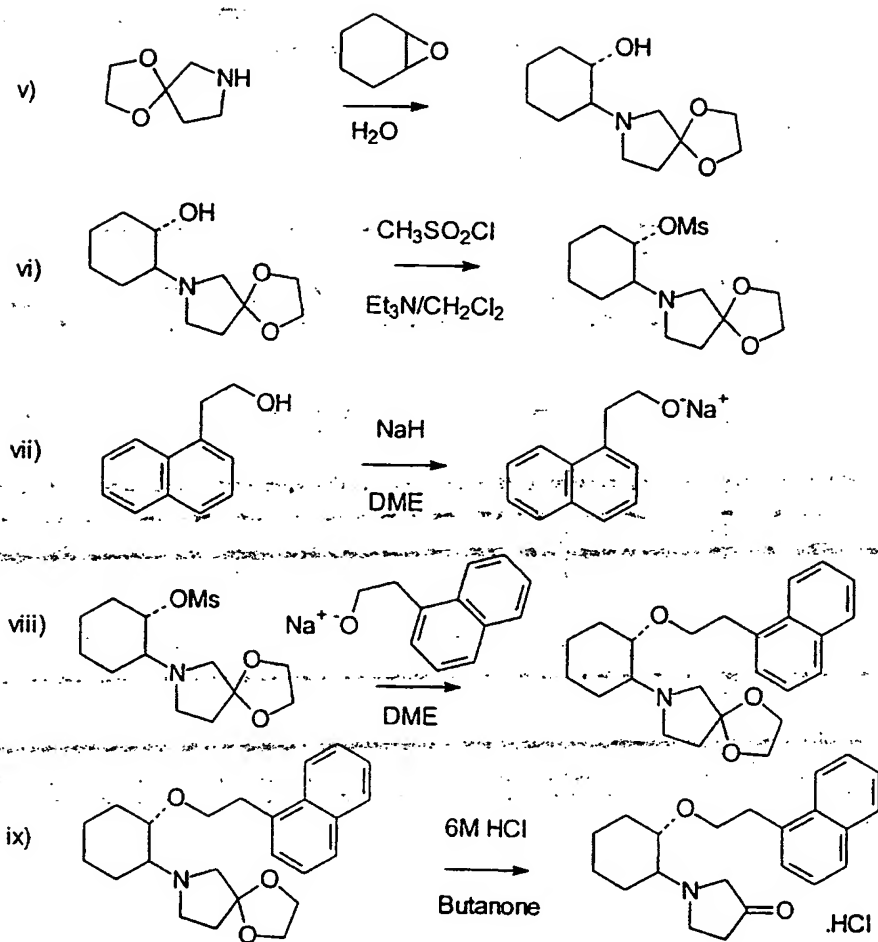


FIG. 4B

INTERNATIONAL SEARCH REPORT

In. ational Application No

PCT/CA 99/00280

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07C217/52 C07D295/096 C07D207/04 C07D333/56 C07D207/24
C07D295/185 C07D277/04 A61K31/13 A61K31/40 A61K31/41
A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07C C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 08544 A (UNIV. BRITISH COLUMBIA) 30 March 1995 see the whole document	1-97
A	WO 93 19056 A (UNIV. BRITISH COLUMBIA) 30 September 1993 see the whole document	1-97

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

15 July 1999

Date of mailing of the international search report

03.08.99

Name and mailing address of the ISA

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Authorized officer

Janus, S

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00280

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91 and 93 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 99/00280

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
effects of the compound/composition.
2. ☒ Claims Nos.: 1-9, 11-97 (all in part)
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

page 2 of 2

INTERNATIONAL SEARCH REPORT

International Application No. PCT/CA 99 00280

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Although claims 17, 19, 21, 23, 25, 27, 29, 31, 33, 35, 37, 39, 41, 43, 45, 47, 49, 51, 53, 55, 57, 59, 61, 63, 65, 67, 69, 71, 73, 75, 77, 79, 81, 83, 85, 87, 89, 91 and 93 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Claims Nos.: 1-9, 11-97 (all in part)

The definition of the general formula (I) is too general and/or encompasses an extremely broad range of totally different chemical compounds, only partly supported by the examples given in the description. The vast number of theoretically conceivable compounds resulting from the combination of all possible substituents precludes a comprehensive search. Guided by the spirit of the application and the inventive concept as disclosed in the description, and in particular in the examples (see also claim 10), the search has been limited to the following cases: R1 and R2 are as defined in formula (XVI) (see claim 9), R3-R5 are hydrogen, A is selected from the list given for formula (XVI) and X is a methylene group or a CH₂-O group, the oxygen atom being attached to group A.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Application No
PCT/CA 99/00280

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9508544 A	30-03-1995	AU 7650294 A CA 2172513 A EP 0720605 A US 5637583 A US 5885984 A	10-04-1995 30-03-1995 10-07-1996 10-06-1997 23-03-1999
WO 9319056 A	30-09-1993	AT 154934 T AU 3882793 A CA 2132841 A DE 69311896 D DE 69311896 T EP 0632806 A ES 2104142 T HK 1000684 A JP 7505151 T US 5506257 A	15-07-1997 21-10-1993 30-09-1993 07-08-1997 16-10-1997 11-01-1995 01-10-1997 17-04-1998 08-06-1995 09-04-1996

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